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AMINO ACID TOLERANCE TESTS IN CHILDREN

HERMAN ANFANGER, M.D.
AND
ROBERT M. HEAVENRICH, M.D.
NEW YORK

THIS study was undertaken to determine the rate of absorption of protein, partially hydrolyzed protein, and amino acids in patients with cystic fibrosis of the pancreas, the celiac syndrome and other conditions.

The disease known as cystic fibrosis of the pancreas has been separated from that group of symptoms commonly referred to as the "celiac syndrome." Siwe [1] first suggested in 1932 that the pancreatic secretions in cystic fibrosis of the pancreas are deficient in trypsin. Andersen [2] noticed the presence of essentially normal levels of trypsin in the duodenal juice in patients with the celiac syndrome. It has, therefore, become the custom to establish the diagnosis of cystic fibrosis of the pancreas by passage of a tube into the duodenum, aspiration of the duodenal contents and demonstration of the absence of trypsin in the duodenal fluid. The finding of an adequate level of trypsin in the aspirated secretions is sufficient to eliminate the diagnosis of cystic fibrosis. The converse, however, is not conclusive, unless the investigator is sure he has obtained pure duodenal juice, and that must be confirmed by lipase studies.

In a patient with adequate secretion of trypsin, one would expect the breakdown of protein in the jejunum and the rise of the amino acid content of the blood. In a patient with a low trypsin level, this breakdown of protein should not occur as rapidly, and consequently, the amino acid level in blood should not rise. To test this hypothesis,

From the Pediatric Service of Dr. Murray H. Bass at Mount Sinai Hospital.

1. Siwe, S. A.: Ueber die exokrine Funktion der Pankreas und die Folgen ihres Wegfalles: Ein Fall von fast totaler Agenesie des exokrinen Teiles des Pankreas, Deutsches Arch. f. klin. Med. **173**:339-358, 1932.

2. Andersen, D. H.: Pancreatic Enzymes in the Duodenal Juice in the Celiac Syndrome, Am. J. Dis. Child. **63**:643-658 (April) 1942. Farber, S.; Shwachman, H., and Maddock, C. L.: Pancreatic Function and Disease in Early Life: I. Pancreatic Enzyme Activity and the Celiac Syndrome, J. Clin. Investigation **22**:827-833 (Nov.) 1943.

we studied the blood alpha-amino nitrogen levels following the ingestion of protein and protein derivatives, as did West, Wilson and Eyles.[3]

METHOD

The test was performed after the patient had fasted for six to eight hours, when the level of blood amino nitrogen was determined. After the fasting period, the test meal was administered and specimens of blood were taken at one-half hour, one hour, two, three, four and five hours. The determination of the blood amino nitrogen was done according to the micro method of Krauel,[4] which has the advantage of requiring only 0.2 cc. of capillary blood.

CURVES FOR AMINO NITROGEN ABSORPTION AFTER INGESTION OF PROTEIN AND PROTEIN DERIVATIVES

A. Absorption of Gelatin.—To study amino nitrogen levels in the blood after ingestion of protein, 24 patients were given solutions of

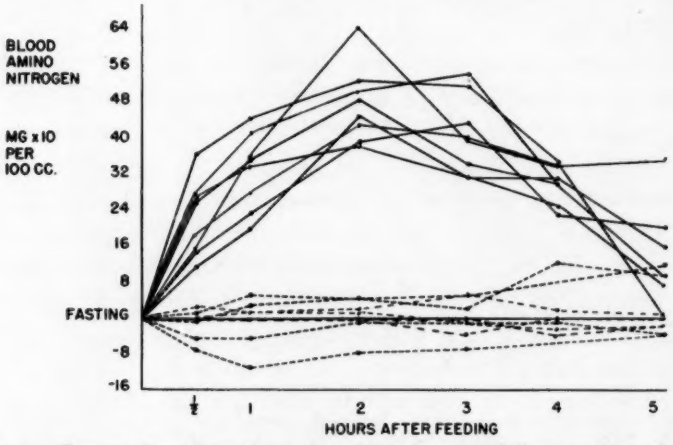

Chart 1.—Curves for absorption of amino nitrogen following ingestion of a test feeding of gelatin. The solid lines indicate values for controls and the broken lines, values for patients with cystic fibrosis of the pancreas.

gelatin. Five had pancreatic fibrosis, for 2 of whom tests were repeated; 1 had pancreatic achylia[5]; 6 had the celiac syndrome, and the others were convalescing from various conditions (chart 1; table 1). The dosage given was 1.25 or 1.75 Gm. per kilogram of body weight dis-

3. West, C. D.; Wilson, J. L., and Eyles, R.: Blood Amino Nitrogen Levels Following Ingestion of Proteins and of a Protein Hydrolysate in Infants with Normal and with Deficient Pancreatic Function, Am. J. Dis. Child. **72**:251-273 (Sept.) 1946.

4. Krauel, K. K.: The Microdetermination of Amino Acid Nitrogen in Blood with the Spectrophotometer and with the Optical Colorimeter, J. Lab. & Clin. Med. **29**:222-227 (Feb.) 1944.

5. This was a boy who had been perfectly well until 9 years of age, when he was proved to have pancreatic achylia by studies of duodenal drainage, enzymes and nitrogen balance and the results of pancreatic biopsy. This will be published as a separate case report.

solved in a volume of liquid that these children were accustomed to take. The gelatin was unflavored and dissolved in hot water. Because of the need for rapid ingestion before it became too thick to pass through a nipple, almost all the feedings were given by gavage to infants and by cup or spoon to older children. No child vomited or had any unusual symptoms. In the chart the curves show only the increment rise above the fasting level. Examination of the curves reveals a decided difference

TABLE 1.—*Amino Acid Nitrogen Levels in the Blood Following Ingestion of Gelatin*

Patient	Age	Amino Acid Nitrogen, Mg. × 10 per 100 Cc. Fasting	½ Hr.	1 Hr.	2 Hr.	3 Hr.	4 Hr.	5 Hr.	Dosage, Gm./Kg.	Diagnosis and Comment
H. Z.	5 mo.	57	50	46	49	50	..	53	1.75	Cystic fibrosis of the pancreas
	1 yr.	43	47	44	45	50	45	44	1.25	7 mo. after previous test
A. F.	6 mo.	48	48	50	53	53	..	60	1.75	Cystic fibrosis of pancreas; meconium ileus
A. P.	11 mo.	58	53	53	56	57	57	54	1.75	Cystic fibrosis of pancreas
	12 mo.	82	82	83	88	81	79	79	1.75	1 mo. after previous test
W. B.	6 mo.	62	63	68	68	64	74	72	1.25	Cystic fibrosis of pancreas; supplemental food given at 4th hour
G. N.	16 mo.	84	84	84	84	79	80	80	1.75	Cystic fibrosis of pancreas
H. F.	9 yr.	80	80	80	80	80	83	83	1.75	Pancreatic achylia
K. G.	8 mo.	42	..	64	84	87	77	62	1.75	Celiac syndrome
D. K.	4 mo.	55	70	70	84	81	66	59	1.25	Celiac syndrome; congenital cardiac disease
T. U.	8 mo.	59	63	80	90	87	83	66	1.75	Celiac syndrome; acute catarrhal otitis media
L. B.	2 yr.	62	110	110	93	85	75	75	1.75	Celiac syndrome
S. M.	2 yr.	90	117	129	135	143	115	110	1.75	Celiac syndrome
M. F.	10 mo.	96	122	128	130	127	120	104	1.75	Celiac syndrome
P. F.	6 yr.	79	94	115	142	118	115	80	1.75	Infection with spirillum minus; malnutrition
N. S.	6 mo.	67	86	90	91	88	85	66	1.75	Congenital cardiac disease
H. C.	4 mo.	58	67	72	91	92	94	89	1.25	Congenital cardiac disease; malnutrition
M. Y.	6 mo.	80	124	133	131	128	108	104	1.75	Diarrhea; convalescent
H. T.	2 mo.	50	76	85	98	84	79	75	1.75	Diarrhea; convalescent
A. G.	4 mo.	55	73	82	97	95	91	93	1.75	Bronchitis; acute suppurative otitis media
L. L.	2 mo.	53	55	60	68	80	..	75	1.75	Congenital syphilis
	3 mo.	46	60	73	85	89	68	66	1.75	1 mo. after previous test
M. M.	2 mo.	65	81	103	99	127	..	90	1.75	Bronchopneumonia; supplemental feeding given at 3d hour
C. S.	3 yr.	56	92	99	106	105	90	..	1.75	Nephrosis; given plasma intravenously at 5th hour
P. R.	2 wk.	58	83	82	113	114	..	..	1.75	Eczema
E. F.	3 mo.	45	56	64	90	75	75	56	1.75	Diaper rash
A. V.	2 yr.	56	67	70	72	71	62	62	1.25	Paratyphoid fever

in blood levels of amino nitrogen. In all the patients, except those with pancreatic fibrosis and pancreatic achylia, absorption was adequate, the amino nitrogen level in the blood beginning to rise in one-half hour and continuing to do so for two to three hours, when it reached its peak and then slowly subsided. In the patients with pancreatic fibrosis, however, as there was no trypsin digestion of the gelatin, the curve was flat with the values for the five hourly specimens not varying much from the original fasting level.

In 3 of the patients with pancreatic fibrosis a small rise in blood amino nitrogen occurred at the fourth to fifth hour. This rise can be

explained better by bacterial decomposition of the gelatin in the intestinal tract, rather than by the theory of larger amounts of trypsin being present in some patients with pancreatic fibrosis.

As was shown by West, Wilson and Eyles,[3] this difference in the curves for amino acid absorption following the ingestion of gelatin is significant enough, statistically, to be used as a specific test to differentiate pancreatic fibrosis from the celiac syndrome.

B. Absorption of Casein Hydrolysate.—When a flat curve for gelatin tolerance is obtained, one must prove that the defect is due to faulty digestion of protein and not to impaired absorption of amino acid. To show that there was no impairment in the absorption of amino acid,

TABLE 2.—*Amino Acid Nitrogen Levels in the Blood Following Ingestion of Protein Hydrolysate*

Patient	Age	Amino Acid Nitrogen, Mg. × 10 per 100 Cc.							Dosage, Gm./Kg.	Diagnosis and Comment
		Fasting	½ Hr.	1 Hr.	2 Hr.	3 Hr.	4 Hr.	5 Hr.		
A. D.	29 mo.	57	59	59	76	70	..	41	2.5	Cystic fibrosis of the pancreas
H. Z.	5 mo.	57	95	86	86	69	..	61	1.75	Cystic fibrosis of the pancreas
A. F.	6 mo.	68	106	113	89	65	77	68	2.5	Cystic fibrosis of the pancreas; receiving pancreatin U. S. P.
N. S.	8 mo.	59	81	71	70	66	62	67	1.75	Eczema
J. L.	3 mo.	58	76	61	72	75	..	44	1.75	Convalescent from pneumonia
M. K.	4 mo.	46	67	68	59	50	40	46	1.75	Pyelitis; vomited at 4th hour
E. V.	1 yr.	59	83	120	133	114	71	67	2.5	Eczema; asthmatic bronchitis
J. O.	6 wk.	75	88	90	94	82	82	86	2.5	Rectal bleeding; foul, watery stool
J. F.	8 yr.	68	81	106	81	76	68	45	1.75	Obstructive jaundice
V. J.	18 mo.	50	110	105	84	74	55	58	1.75	Convalescent from pneumonia
V. K.	30 mo.	60	83	86	76	59	65	53	1.75	Infection of upper respiratory tract; did not take all of feeding well
S. H.	8 mo.	67	107	142	106	93	76	58	2.5	Convalescent from pneumonia
C. S.	10 mo.	70	75	82	82	90	77	75	2.5	Allergy; vomited and had loose, watery stool
V. T.	6 mo.	62	89	78	85	116	..	65	1.0 ?	Bronchiolitis; offered 2.5 Gm./Kg.; vomited
E. C.	3 yr.	67	93	93	68	69	..	65	1.75	Malnutrition; took feeding slowly

3 patients with cystic fibrosis and 12 other patients either convalescing or with other conditions were tested after the administration of a protein hydrolysate [6] which contained, on an average, 40 per cent amino acids (table 2). The ages ranged from 2 months to 3 years. The amount given was 1.75 or 2.5 Gm. per kilogram of body weight dissolved in a volume of water which the patients were accustomed to take. The feedings were either taken voluntarily by the child or given by gavage if the mixture was not well taken. The older the child, the more frequently gavage was necessary, as the taste of the hydrolysate was unpleasant. Three children vomited during the course of the test, and 2 others had loose, watery stools, with an odor resembling the original

6. The preparation used was aminonat,® which has the following composition: protein hydrolysate, 94 per cent; total protein equivalents, 70 per cent; total nitrogen, 11.2 per cent, and amino acids, 40 per cent.

ingested mixture (chart 2). In order not to overload the chart, only four typically normal curves and two for patients with cystic fibrosis are included. It is apparent from inspection of the chart that there was no real difference in the type of curves for the normal persons and for those with pancreatic fibrosis. The reason for similar types of curves in all patients studied is apparent, since the protein hydrolysate contained enough amino acids per se to be absorbed rapidly and to produce an adequate rise in blood amino nitrogen. Because the test substance was already hydrolyzed, there was no need for trypsin action. As can be seen from the curves, the amino acids were adequately absorbed by all patients and, therefore, such a test meal is not specific for diagnosis of cystic fibrosis of the pancreas but may be used to demonstrate normal absorption of amino acid.

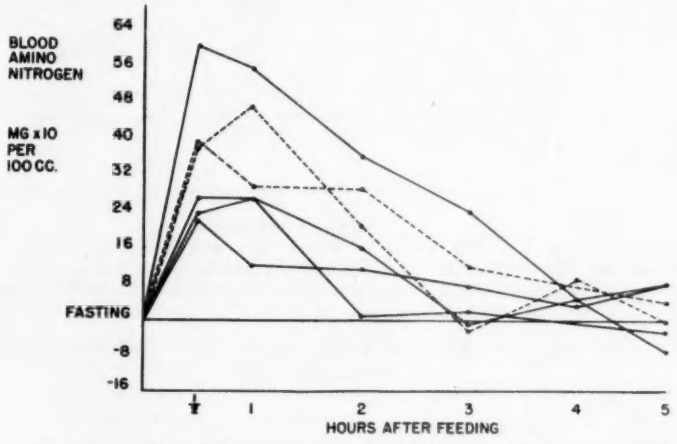

Chart 2.—Curves for absorption of amino nitrogen following ingestion of a test feeding of casein hydrolysate. The solid lines indicate values for controls and the broken lines, values for patients with cystic fibrosis of the pancreas.

C. Absorption of Aminoacetic Acid.—As we encountered difficulty in administering protein hydrolysate to babies—some disliked its taste, vomited or had diarrhea—it occurred to us to try instead a single amino acid. Aminoacetic acid (glycine) was chosen, since it is readily available, is taken by all children and does not give rise either to vomiting or to diarrhea (chart 3 and table 3). It was tried by several investigators on adults in rather large doses without deleterious effect. The dosage we used was 1.0 to 1.75 Gm. per kilogram of body weight, and it was given to 2 patients with pancreatic fibrosis, to 1 with pancreatic achylia and to 6 who were convalescent. As would be expected from the fact that no enzymes are needed to break down the food prior to absorption, the curves show no significant differences. The rise of the individual curve is rather steep, reaches its maximum in about two hours and then declines to the fasting level in about five hours.

Instead of the five hour test as done, a two or three hour test is probably all that is necessary to demonstrate that a patient has normal ability to absorb amino acids. For this purpose, aminoacetic acid proved a better test substance than protein hydrolysate.

D. Curves for Absorption of Aminoacetic Acid and Gelatin.—As has been explained, when a flat curve for gelatin tolerance is obtained, it

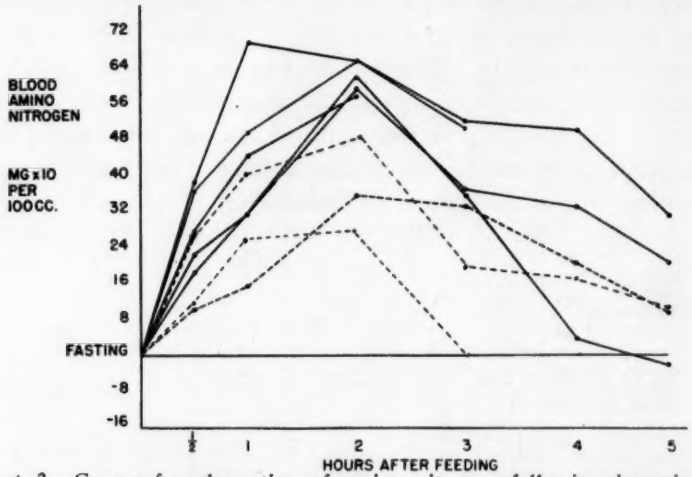

Chart 3.—Curves for absorption of amino nitrogen following ingestion of a test feeding of aminoacetic acid. The solid lines indicate values for controls and the broken lines, values for patients with cystic fibrosis of the pancreas.

TABLE 3.—*Amino Acid Nitrogen Levels in the Blood Following Ingestion of Aminoacetic Acid*

Patient	Age	Amino Acid Nitrogen, Mg. × 10 per 100 Cc. Fasting	½ Hr.	1 Hr.	2 Hr.	3 Hr.	4 Hr.	5 Hr.	Dosage, Gm./Kg.	Diagnosis and Comment
A. P.	11 mo.	43	53	58	78	75	63	52	1.25	Cystic fibrosis of the pancreas
G. N.	1 yr.	70	80	94	95	70	70	70	1.25	Cystic fibrosis of the pancreas
H. F.	9 yr.	75	101	115	123	93	91	85	1.75	Pancreatic achylia; vomited at 3d hour
J. S.	10 mo.	69	105	117	135	119	..	..	1.25	Gastroenteritis
H. P.	5 mo.	65	103	134	130	116	114	95	1.25	Convalescent from pneumonia
S. S.	9 mo.	54	72	85	112	90	86	74	1.25	Anorexia; feeding problem
R. C.	7 yr.	56	78	87	117	90	59	54	1.00	Rheumatic fever
E. F.	4 mo.	48	75	92	105	..	..	..	1.25	Convalescent from pneumonia
C. M.	2 mo.	51	72	92	75	..	..	..	1.0	Convalescent from bronchiolitis

is necessary to follow this test with another one, with the use of aminoacetic acid to demonstrate that the flat curve is due to faulty trypsin action and not to impairment of absorption of amino acids. Obviously, if these two tests could be combined, there would be considerable saving of time and energy. It has been pointed out that when aminoacetic acid is used alone, the maximum level of blood amino nitrogen occurs during the first and second hours; while after gelatin, the peak is between the second and fourth hours. When aminoacetic acid and gelatin are

administered simultaneously to persons without cystic fibrosis, one would expect, therefore, two rises in the blood amino nitrogen resulting from early absorption of aminoacetic acid and later absorption of gelatin. When the combination of aminoacetic acid and gelatin is

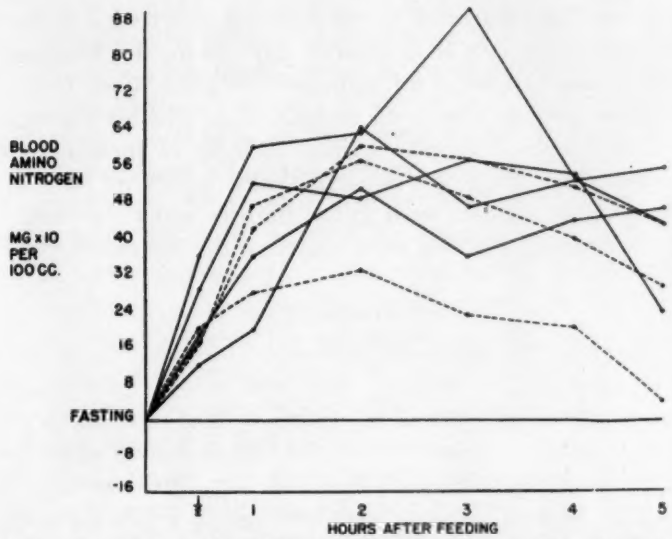

Chart 4.—Curves for absorption of amino nitrogen after ingestion of a mixture of aminoacetic acid and gelatin. The solid lines indicate values for controls and the broken lines, values for patients with cystic fibrosis of the pancreas.

TABLE 4.—*Amino Acid Nitrogen Levels in the Blood Following Ingestion of Equal Parts of Aminoacetic Acid and Gelatin*

Patient	Age	Amino Acid Nitrogen, Mg. × 10 per 100 Cc. Fasting	½ Hr.	1 Hr.	2 Hr.	3 Hr.	4 Hr.	5 Hr.	Dosage, Gm./Kg.	Diagnosis and Comment
W. B.	4 mo.	60	81	102	120	117	111	106	1.0	Cystic fibrosis of the pancreas
A. P.	11 mo.	59	77	106	116	108	99	89	1.0	Cystic fibrosis of the pancreas
A. D.	2 yr.	64	83	92	97	87	75	68	1.0	Cystic fibrosis of the pancreas
M. P.	1 yr.	37	45	51	40	50	47	47	1.0	Celiac syndrome
B. D.	2 yr.	38	67	90	77	95	90	62	1.25	Celiac syndrome
D. L.	6 wk.	54	90	114	117	144	107	97	1.0	Normal child
W. M.	6 wk.	54	67	85	100	100	73	70	1.0	Congenital malrotation of small intestine; convalescent after operation
M. P.	15 mo.	41	54	61	105	88	94	97	1.0	Bronchitis; fractured skull
P. T.	1 yr.	58	78	94	109	94	102	105	1.0	Acute suppurative otitis media; conjunctivitis

given to patients with cystic fibrosis, on the other hand, as there is no trypsin activity, the secondary rise due to gelatin absorption should be absent. One should obtain a curve similar to that seen when aminoacetic acid alone is the test substance, the curve reaching its peak in two hours and then dropping constantly for three hours.

The mixture of aminoacetic acid and gelatin was given to 9 patients, 3 of whom were normal; 2 had the celiac syndrome; 3 had pancreatic

fibrosis, and 1 had had partial intestinal resection on operation. The dosage given was 1 Gm. of gelatin and 1 Gm. of aminoacetic acid per kilogram of body weight. Almost all the feedings were given by gavage and were well tolerated (chart 4 and table 4).

The four curves shown on chart 4 for the persons without cystic fibrosis reveal the occurrence of the expected effect with an initial rise in one to two hours; the level remains elevated for five hours or shows a secondary peak in the third and fourth hours. When this test was performed on patients with cystic fibrosis of the pancreas, the secondary peak was absent as expected. Critical analysis of these curves, however, reveals that there are no statistically significant differentiating features between patients with cystic fibrosis and those with normal pancreatic function. Further modification of this combined test is being undertaken.

COMMENT

The diagnosis of congenital fibrosis of the pancreas is one which should be suspected in a young child who fails to gain properly and who has recurrent episodes of bronchitis with or without the presence of foul, fatty stools. Andersen [7] showed that in infants under 6 months of age with pancreatic fibrosis typical foul, fatty stools are not common. It is usually after 6 months, when new foods are being added, that stools tend to become typical of the disease. It is important that the diagnosis of cystic fibrosis of the pancreas be made as early as possible in order that proper treatment be instituted to prevent the pulmonary changes which usually lead to a fatal termination.

The diagnosis of pancreatic fibrosis has, until recently, been confirmed only by the failure to find trypsin in the aspirated duodenal secretion after duodenal intubation. Unless done by an experienced staff, this procedure is fraught with many difficulties. It is time consuming, necessitating the operator to be in almost constant attendance and to observe the passage of the tip of the tube under fluoroscopic control. The separation of the x-ray room and the pediatric ward in practically all hospitals and the restriction of the usually busy fluoroscopy room are obvious difficulties of this method. Although everyone now realizes the dangers of excess radiation, still there is a tendency for the overzealous physician occasionally to overexpose either the child or himself.

The finding of an adequate level of trypsin in the aspirated secretion is sufficient to eliminate the diagnosis of cystic fibrosis. The converse, however, is not conclusive, unless the investigator is sure he has obtained pure duodenal juice, and that must be confirmed by lipase studies. The mere presence of an alkaline reaction of the aspirated

7. Andersen, D. H.: Celiac Syndrome: Fecal Excretion in Congenital Pancreatic Deficiency at Various Ages and with Various Diets, with Discussion of the Optimal Diet, Am. J. Dis. Child. **69**:221-230 (April) 1945.

liquid is not final proof that the tube is in the duodenum and that only duodenal juice has been obtained. Duodenal reflux may occur, which may change the p_H of the gastric contents enough to give an alkaline reaction. This may be especially significant in a child with enteritis who has a low acid content in the gastric juice. Furthermore, the p_H of the gastric fluid is higher in infants than in older children, ranging between 4 and 5. Finally, it is difficult to obtain even a small amount of secretion for the determination of trypsin in young subjects, for, as shown by Kajdi and Davison,[8] the rate of formation of pancreatic secretion during feeding not only varies from time to time but even in health is small, ranging from only 4 to 13 cc. per hour. In very young infants, on the other hand, or in the presence of diarrhea, dehydration or marasmus, even this small amount is decreased.

Various other methods have been tried to establish the diagnosis in a positive sense. The presence of undigested meat fibers in stools is suggestive of the disease but not conclusive, however, since in diarrhea or malnutrition undigested particles are frequently seen. This test, too, is applicable only to older children taking meat in their diets and not to infants on a milk diet.

Andersen [7] showed that the absence of microscopic fat from feces of children on normal diets is adequate evidence for ruling out pancreatic deficiency. Conversely, the finding of fat in stools simply means that there is poor digestion or absorption of the substance, and this occurs in the celiac syndrome, as well as in cystic fibrosis. Tests for vitamin A absorption, using vitamin A in an oily menstruum, have been tried, but, as shown by May and McCreary,[9] absorption of such vitamin A is low in persons with either pancreatic fibrosis or celiac disease. These diseases cannot be differentiated by this means. It was also shown that a low curve for vitamin A is not even diagnostic of these diseases, since a low rate of absorption is observed in persons with other conditions, such as allergy, nonspecific diarrheas and malnutrition. Therefore, if another method can be discovered which will accurately establish a diagnosis of cystic fibrosis without the moving of the child away from the pediatric ward or the requirement that a tube remain in place for hours, it is to be preferred. West, Wilson and Eyles [3] first published a method dependent on the digestion and absorption of amino acids and proteins which obviates these faults and establishes accurately the diagnosis of cystic fibrosis of the pancreas.

8. Kajdi, L., and Davison, W. C.: Chemical and Enzymic Studies of the Duodenal Contents of Infants, J. Pediat. **23**:204-214 (Aug.) 1943.

9. May, C. D., and McCreary, J. F.: Absorption of Vitamin A in Celiac Disease: Interpretation of Vitamin A Absorption Test, J. Pediat. **18**:200-209 (Feb.) 1941.

The gelatin tolerance test eliminates the necessity of passing a duodenal tube and has been shown to be just as diagnostic as determination of trypsin. In a child without a pancreatic deficiency disease, after gelatin ingestion, a typical rise in blood amino acids is evident, reaching a peak in two to four hours and descending almost to the fasting level in five hours. In a patient with pancreatic disease, this typical rise is absent and a flat curve occurs, which may show a slight rise at the fourth and fifth hours. This rise is probably not due to the presence of trypsin in large amounts, since varying degrees of pancreatic deficiency have never been shown. It is probably the result of the action of intestinal bacteria on the gelatin, with slow liberation of amino acids.

After a flat curve for gelatin tolerance has been observed, it is important to rule out the possibility of poor absorption of amino acid as the cause of such a curve. For this, West and his associates [3] used a protein hydrolysate. Our observations confirmed theirs, namely, that the administration of a protein hydrolysate produced a rise in blood amino acids in all children. No significant difference was seen between normal children and those with pancreatic fibrosis. Thus, protein hydrolysate may not be used as a test substance for the diagnosis of cystic fibrosis, but may be used to demonstrate amino acid absorption.

Because protein hydrolysate had an unpleasant taste for older children, and because it produced nausea and vomiting, a search was made for a more satisfactory substance to be used to demonstrate amino acid absorption. Aminoacetic acid proved to be an ideal test substance. It was taken without difficulty and was well tolerated by all children, who liked its sweet taste. It was rapidly absorbed, producing a high level of blood amino nitrogen within two hours after administration, after which time the blood content gradually fell to the fasting level. When aminoacetic acid is used to demonstrate amino acid absorption, therefore, it is necessary to collect specimens of blood for only two or three hours. Because of these numerous advantages, aminoacetic acid proved to be considerably more satisfactory than casein hydrolysate.

An attempt was made to perform the gelatin tolerance test and the aminoacetic acid test simultaneously. In all normal patients, the anticipated curves were obtained, with an early rise in blood amino nitrogen from the absorption of aminoacetic acid, followed by either a sustained high level in the blood or a secondary peak due to the digestion of gelatin. When the test was performed on patients with cystic fibrosis of the pancreas, the secondary peak due to gelatin digestion was absent, but the shape of the curves obtained was not adequately different from those of normal controls to be characteristic of cystic fibrosis. Further variation of this combined test is being undertaken. For the present, however, we find it necessary to use gelatin and aminoacetic acid in separate tests.

There were no technical difficulties in performing the amino acid studies. The determination of the blood amino nitrogen was done according to the micro method of Krauel,[4] which has the advantage of requiring only 0.2 cc. of capillary blood. Duplicate or triplicate specimens were drawn to eliminate possible errors in chemical determination. Blood was drawn from the finger, toe or heel. It is essential that a free flow of blood be obtained. This can be done by first warming the child's finger or heel and then making one or two moderately deep punctures with a blood lancet. A free flow of blood is important, since the concentration of amino acids in the tissues is approximately five to ten times as great as that in the blood. There is an exchange of amino acids among the tissues, extracellular fluid and the blood, as shown by Van Slyke and Meyer.[10] The tissues take up amino acids rapidly when their concentration is increased in the blood and give them up to the blood again when the concentration is decreased. There is distinctly more amino acid nitrogen in the blood cells than in the plasma. Van Slyke and Meyer demonstrated from 3.4 to 5.5 mg. per hundred cubic centimeters in plasma but from 6.5 to 9.0 mg. per hundred cubic centimeters in cells. According to Becher and Herrmann,[11] leukocytes contain more than erythrocytes. The difference depends not on a diffusion equilibrium but on the vital activities of the cells.

Estimation of the blood amino nitrogen has been made with several methods. Hamilton and Van Slyke's [12] ninhydrin–carbon dioxide procedure, although accurate, is difficult. With this test, levels of normal blood amino nitrogen vary between 3.4 and 4.9 mg. per hundred cubic centimeters. Folin and Wu's [13] colorimetric method, using naphthoquinone and sulfonic acid, is simpler and gives a normal blood level of 5.0 to 8.0 mg. per hundred cubic centimeters. Krauel [4] adapted this colorimetric method to micro determinations and showed it to be reproducible. It is unimportant in our study that the colorimetric determinations differ from the gasometric ones, since it is the degree of rise in blood amino nitrogen that interests us and not the absolute amount.

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10. Van Slyke, D. D., and Meyer, G. M.: The Amino Acid Nitrogen of the Blood: Preliminary Experiments on Protein Assimilation, J. Biol. Chem. **12:** 399-410, 1912.

11. Becher, E., and Herrmann, E.: Der freie und gebundene Aminostickstoff im enteiweissten Blut und Gewebe unter normalen und pathologischen Verhältnissen, Deutsches Arch. f. klin. Med. **173:**1-22, 1932.

12. Hamilton, P. B., and Van Slyke, D. D.: The Gasometric Determination of Free Amino Acids in Blood Filtrates by the Ninhydrin-Carbon Dioxide Method, J. Biol. Chem. **150:**231-250 (Sept.) 1943.

13. Folin, O., and Wu, H.: A System of Blood Analysis: A New Colorimetric Method for the Determination of the Amino-Acid Nitrogen in Blood, J. Biol. Chem. **51:**377-391 (April) 1922.

CONCLUSIONS

There are now two technics which may be employed to establish the diagnosis of cystic fibrosis of the pancreas. The first is the demonstration of absence of trypsin in the aspirated duodenal fluid. The difficulties in performing this test have been enumerated. The second test, which is simpler, and even more reliable, is the demonstration of failure of trypsin digestion of protein in vivo, as evidenced by the failure of the blood amino acid to rise after gelatin has been ingested. That this flat curve for amino acid is not due to faulty amino acid absorption must be shown by a rise in the blood amino nitrogen after ingestion of a protein hydrolysate or an amino acid. Protein hydrolysate produced nausea and vomiting and its use, therefore, was discontinued. Aminoacetic acid, however, proved to be an ideal substance to demonstrate amino acid absorption.

SUMMARY

1. Patients with cystic fibrosis of the pancreas, pancreatic achylia and the celiac syndrome and others convalescing from acute illnesses were given gelatin, protein hydrolysate, aminoacetic acid (glycine) and a combination of gelatin and aminoacetic acid orally, and the blood amino acid (amino nitrogen) levels were studied.

2. Gelatin produced a good rise in the amino nitrogen level in all patients, except those with cystic fibrosis of the pancreas and pancreatic achylia, in whom a flat curve diagnostic of these diseases was obtained.

3. Protein hydrolysate produced a good rise in amino nitrogen in all patients studied, but was discarded because of difficulty in administration and untoward reaction.

4. Aminoacetic acid also produced a good rise in amino nitrogen in all patients, was easily administered without untoward reaction and was used to rule out the possibility of impaired absorption as the cause of a flat curve for amino nitrogen.

5. A mixture of gelatin and aminoacetic acid, as used, produced curves for amino nitrogen which could not be employed to differentiate cystic fibrosis of the pancreas from the celiac syndrome.

Miss Francis Cohen, A.B., and Mr. Richard L. Fenichel, A.B., assisted technically in this study.

888 Park Avenue (21).

EPIDEMIC OF DIPHTHERIA IN ATHENS, GREECE, DURING THE WINTER 1946-1947

C. CHOREMIS, M.D.
N. ZERVOS, M.D.
K. PADIATELLIS, M.D.
P. PAPADIMITROPOULOS, M.D.
AND
M. NIKOLETTOU, M.D.
ATHENS, GREECE

FROM April 1946 to April 1947, the patients with diphtheria treated in the Children's Hospital of the National University numbered 551.

In the winter of 1945, an increase in the incidence of diphtheria was already apparent in Athens and its suburbs, since in that year the patients treated in the Children's Hospital of the National University exceeded 350. We do not intend to deal with the epidemiology of the disease or with the conditions under which it may develop or can be checked, but the increase of patients noted in 1945-1946 indicated that the occurrence of an epidemic of diphtheria was very likely.

A. DIPHTHERIA IN GREECE, 1854-1934

Indeed, when comparing the admission of patients to the hospital for 1922 and the following years, which has now been statistically recorded, we noticed a progressive increase of those with diphtheria. Accurate statistics for previous years are missing. Reverting to the past,[1] we found the first description of the disease in our country in 1854. After this date, only sporadic cases are recorded until 1863. In 1870, an obvious increase in diphtheria was noted, which, in two years' time, assumed the character of an epidemic in Athens. On this outbreak accurate statistical data are lacking. In 1873-1874, a decrease in incidence of the disease was observed. In the last twenty years,[2] the total number of patients treated for diphtheria was 2,502.

From the Pediatric Clinic of the Medical School of the University of Athens.

1. Choremis, C.: Diphtheria, in Proceedings of the Athens Medical Society, 1930, p. 476.

2. Charocopos and Colocouri: Diphtheria Statistics, Greek M. Mag., Thessaloniki **3**:20, 1947.

From these figures, the extent of the epidemic in 1946-1947 is shown clearly. They would probably be still larger if they included data on the incidence in the provinces, information which, as a consequence of the wretched state of communications and the civil war, it has not been possible to convey to Athens.

The increase in diphtheria in Greece is certainly not independent of that prevailing in the other European countries. Indeed, in the last few years the incidence increased to a degree that may be called epidemic. To this increase, the last World War most certainly contributed. Further, during the last World War diphtheria in Europe [3] constituted the predominant childhood disease from the standpoint of sickness and death rates. From statistics published up to date, in Germany during 1942 the number of deaths from diphtheria

TABLE 1.—*Incidence of Diphtheria in Greece, 1922 to 1932*

Year	No. of Cases Reported	Mortality, Percentage
1922	5	0
1923	16	31.0
1924	8	50.0
1925	13	15.3
1926	19	42.1
1927	45	8.8
1928	39	2.6
1929	59	13.5
1930	72	18.0
1931	128	12.4
1932	142	17.6

was 15,000. In 1943, 300,000 cases were reported. Likewise, in 1942, 150,000 cases occurred in the Netherlands, with a mortality of 7 per cent.

The increase in diphtheria [4] becomes more obvious if it is taken into consideration that 168,354 cases were observed in twelve European countries from 1928 to 1938, while in 1943 alone 501,911 such cases were reported in these same countries.

As we previously mentioned, the number of cases of diphtheria in Athens, its suburbs and the other provinces of Greece for the period of eleven years,[5] from 1922 to 1932, rose to 546. The incidence for each year is shown in table 1.

3. Stowman, K.: The Epidemic Outlook in Europe, Brit. M. J. **1**:742, 1945.

4. Third issue of the U. N. R. R. A. Epidem. Bull., April 1945.

5. Makkas, G., and Charocopos: Diphtheria Statistics, Arch. Pediat. Clin. **1**:331, 1935.

With respect to anatomic localization, the percentage of the cases is shown in the tabulation.

Percentage of Cases	Localization
38.4	Pharynx
28.2	Mixed—pharynx and larynx
30.0	Larynx
9.0	Nose
5.0	Various other localizations

In 1933-1934, 318 patients were treated, with a mortality of 17.29 per cent.

B. THE EPIDEMIC OF 1946-1947

Within the twelve month period from April 1, 1946, when we took charge of the Children's Hospital, until April 31, 1947, a total of 551 patients with diphtheria were received. They came from the following localities:

No. of Patients	Locality
192	The city of Athens
144	Its neighboring settlements
138	Piraeus and its settlements
77	Various provincial towns and the islands

In respect to the settlements of Athens, the greater number of patients recorded were from (1) Peristeri, with 30, and (2) the Gunpowder Works Settlement, with 27. The number of patients treated from other settlements was fairly below these figures. Finally, from the settlements of Piraeus, Palaia Kokkinia had 20 patients and Nea Kokkinia 17.

TABLE 2.—*Anatomic Localization of Diphtheria*

Localization	Number of Patients	Percentage of Patients
Pharynx	267	48.4
Mixed—pharynx and larynx	74	13.4
Larynx	188	34.3
Nose	14	2.3
Genitals	4	0.7
Skin	1	0.1
Mouth	2	0.3
Postdiphtheritic paralysis	1	0.1

With respect to localization of the disease, the patients in this epidemic should be classified as in table 2.

This table leads us to the conclusion that the percentage of patients with laryngeal diphtheria, in comparison to the percentage previously treated in the Children's Hospital, fluctuates within the same approximate limits; that is, for 1946-1947, 47.7 per cent of the patients had laryn-

geal diphtheria, while from 1922 to 1942, 45.4 per cent of patients had this type. In the period 1922 to 1942, of a total of 2,502 persons with diphtheria, 1,137 had the laryngeal type.[6]

In regard to the day of illness on which admission to the hospital took place, relative data are given in table 3. From this table it may be gathered that most of the patients were admitted on the third day of illness, followed in order by those on the second and fifth days. Four patients with pharyngeal diphtheria entered on the fifteenth day

TABLE 3.—*Admissions of Patients with Diphtheria to the Hospital According to Day of Illness and Type of Disease*

Pharyngeal diphtheria															
Date of illness	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
No. of patients	2	28	55	70	30	25	90	15	10	2	2	2	2	2	4
Deaths	..	..	2	..	1	..	..	1	1	..	1	..	..	..	..
Laryngeal diphtheria															
No. of patients	7	45	60	50	35	30	15	12	..	4	..	3	1	..	..
Deaths	1	2	7	12	3	..	1	..	..	..	..	..	..	..	..

TABLE 4.—*Total Number of Days in the Hospital for Patients with Various Types of Diphtheria*

Month	Pharyngeal Diphtheria, Number of Hospital Days	Laryngeal Diphtheria, Number of Hospital Days	Nasal Diphtheria, Number of Hospital Days	Total Number of Hospital Days
April	137	62	20	218
May	32	48	10	65
June	21	82	..	103
July	95	123	..	218
August	120	39	..	159
September	100	80	30	210
October	340	180	..	520
November	260	140	..	400
December	400	475	..	875
January	320	290	..	610
February	180	280	..	460
March	120	60	20	200
Total	2,125	1,854	80	4,059

of illness. For these patients, although they had been neglected, the outcome was favorable; that is, they were cured.

Number of Days in the Hospital.—The total number of days in the hospital for persons with the various types of diphtheria is shown in table 4. The greatest number of hospital days are shown for December, during which month most of the patients were received in the hospital. The total of 4,059 days amounts to 7.3 days per patient.

6. Vegiloulis, A., and Talides, F.: Diphtheria Statistics, Arch. Pediat. Clin. **2**:187, 1937.

Number of Patients Who Entered Per Month.—The number of patients who entered the hospital per month during the period from April 1946 to March 1947 is presented in table 5.

From table 5, it may be seen that the number of admissions started to increase gradually after April 1946. The climax was reached in the months of November and December. Undoubtedly, this is a proof of the unfavorable influence of weather conditions as regards increase of the disease. Thus, each regional fall of temperature intensified the epidemic. An example of this is the decided increase in the number of patients with diphtheria who were received in the hospital after the sudden fall of temperature last Easter (1947).

TABLE 5.—*Admissions to the Hospital, According to Month of Admission and Localization of Diphtheria*

	Localization								
Month	Larynx	Pharynx	Mixed—Larynx and Pharynx	Nose	Trachea	Genitals	Skin	Mouth	Total
April.....	6	7	..	2	..	..	..	..	15
May.....	3	8	..	1	..	..	..	..	12
June.....	3	8	..	..	..	..	..	..	11
July.....	6	10	..	..	2	..	..	..	18
August.....	2	13	..	..	..	..	..	..	15
September...	11	14	..	2	5	..	..	..	32
October.....	21	41	4	2	..	..	..	..	68
November....	22	43	24	2	..	2	..	1	94
December....	35	38	28	2	13	..	1	..	117
January.....	39	30	14	2	2	..	..	1	88
February....	11	29	4	1	4	2	..	..	29
March.....	3	26	..	..	..	..	..	..	29
Total....	162	267	74	14	26	4	1	2	551

C. ACTIVE INOCULATION

We paid special attention to the problems related to the development of the epidemic. This research, indeed, shows that of 551 patients, only 4 were vaccinated, that is, 0.3 per cent, and the outcome in all of them was favorable. Among these, the first child, aged 14, had a light attack of pharyngeal diphtheria. He had been vaccinated six months previously and entered the hospital on the fourth day of the disease. The second, aged 2, also had a light attack of diphtheria. Admission was on the ninth day of illness. He had been vaccinated a year before and was cured. The third, aged 18 months, had severe laryngeal diphtheria. Admission was on the third day of illness. He was vaccinated ten months previously and was also cured.

D. LARYNGEAL DIPHTHERIA

Among the various forms of the disease, laryngeal diphtheria more particularly burdened the hospital, and we think it proper to discuss this form, as well as the therapy applied. Of 262 patients, it was necessary to use intubation in 66. In 44 patients, the procedure was carried out immediately after admission to the hospital; in 7 patients, twenty-four hours, and in 5, thirty-six hours, after admission. In 1 patient, we proceeded to immediate tracheotomy because intubation could not be successfully performed owing to a bad tumor. This patient was an infant 12 months of age. Intubation was carried out thirteen days later, and he finally was cured. Among those patients in whom intubation was used, 25 showed no relief from it and had finally to be submitted to tracheotomy. The number of patients treated with intubation and the mortality per age group are shown in table 6. The youngest infant subjected to intubation was 6 months old, and he died. The oldest child was 7 years of age. The number of cases

TABLE 6.—*Patients Treated with Intubation and Number of Deaths, According to Age Group*

	Months	Years										
Age	0 to 12	2	3	4	5	6	7	8	9	10	11	Total
No. of patients	12	30	14	4	1	1	3	..	1	..	..	66
Deaths	7	8	2	..	..	1	..	..	..	..	..	18

of laryngeal diphtheria with peril of suffocation in children of more advanced age proves the gravity of the epidemic. The longest duration of the application of intubation was in a boy, 3 years of age, who was subjected, in twelve days' time, to 4 intubations. On the thirteenth day tracheotomy was performed. On the twenty-fifth day he was relieved of the tube and the outcome was favorable. The shortest application of intubation was for twenty-four hours in a child 7 years old.

E. THERAPY

The discovery of the antitoxin treatment and its application in 1894 was one of the most important steps toward progress in the therapy of diphtheria. However, since the initial use of the serum, a notable variation has prevailed in its posology. In older treatises, those of twenty-five years ago, small doses of serum, such as 200 to 500 units per kilogram of body weight, were considered sufficient. Thus, various American writers[7] once recommended 5,000 to 6,000

7. Holt, E. L., and Howland, J.: Diseases of Infancy and Childhood: A Textbook for the Use of Students and Practitioners, ed. 11, New York, D. Appleton-Century Company, Inc., 1940, p. 1092.

units of serum for children under 2 years of age, 7,000 to 8,000 units for children over 2 years and in those seriously ill, 15,000 to 20,000 units. Others [8] recommended 4,000 to 8,000 units per kilogram of body weight in light attacks, subcutaneously or intramuscularly, and 10,000 to 30,000 units in serious cases, intravenously. Other writers [9] based the quantity of the serum on the extent and apparent age of the membrane and the indications of toxemia, large doses being more successful and of more prolonged value than small ones. In nasal diphtheria, for instance, 8,000 to 16,000 units is advised, while in laryngeal and pharyngeal diphtheria 16,000 to 32,000 units per kilogram of body weight is recommended.[10] The others suggested 50 to 100 units per kilogram in slightly ill children, 500 units in those seriously ill, intramuscularly or intravenously, and 100,000 units in children with a positive reaction to the Schick test. The intravenous method is applied only in serious conditions and cases.

Bie,[11] of Copenhagen, administered 300,000 to 500,000 units, and even 800,000 units in more serious cases. Comby administered 40,000 to 60,000 units and continued with 20,000 daily on each remaining day of illness. Lesne, in simple diphtheritic angina, gave 500 units or less, per kilogram of body weight for four to five days, and in serious cases 1,000 units per kilogram for five, six or seven days. Debre-Rámon and Bernard recommended only one injection of serum, according to age, weight and seriousness of attack, of between 15,000 and 50,000 thousand units. Schick, Kassowitz and Budacchi were of the opinion that 500 units per kilogram of body weight should be the maximum dose given.

In our hospital, the opinion prevailing on this matter was always toward using large doses of serum. Without exception, in all our patients we instituted the antitoxin treatment as soon as they entered the hospital, even in those in which the disease was not yet distinctive, instead of waiting twenty-four hours until the result of the bacterial culture was known. The use of serum for 551 patients had the following effect:

In 79 patients, whose condition was considered serious, the serum was inoculated intravenously. In 50 of these condensed serum was

8. Dunlop, D. M.; Davidson, L. S. P., and McNee, J. W.: Textbook of Medical Treatment, ed. 4, Edinburgh, E. & S. Livingstone, 1946, p. 16.

9. Conybeare, J. J.: Textbook of Medicine, ed. 6, Edinburgh, E. & S. Livingstone, 1942, p. 20.

10. Schick, B.: Diphtheria, in Litchfield, H. R., and Dembo, L. H.: Therapeutics of Infancy and Childhood, ed. 3, Philadelphia, F. A. Davis Company, 1947, chap. 24, p. 563.

11. Cited by Nobécourt, P., and Babonniex, L.: Traité de médicine des enfants, Paris, Masson & Cie, 1934, vol. 2, p. 253.

used and in the remaining patients, a mixture of condensed serum and serum from the Institute Pasteur (a complete serum containing 300 antitoxic units per cubic centimeter). In 125 patients, inoculation was intramuscular with the mixed serums and in the remaining 297 with 20,000 units of condensed serum from an American manufacturer.

In comparing the results obtained with the antitoxin treatment, one notes that of 79 patients treated by intravenous inoculation of serum 3 died. We are under the impression that through the Pasteur serum we had the most satisfactory results. The doses we utilized were sufficiently large. We noted that in most patients between the second and the third day of illness the condensed serum from the United States produced a local serum immunity. Penicillin was administered simultaneously with the antitoxin treatment. We were prompted to use this combination by statements in the literature in which penicillin was shown to reenforce the serum action, and further with the consideration that the gravity of the condition was due not only to the diphtheria bacteria but also to ensuing infections of the respiratory organs, occurring mostly after tracheotomy.

Stenosis of the Larynx.—Stenosis of the larynx is the most serious complication of diphtheria. When facing such a condition, the first concern should be to do whatever possible with all natural and pharmaceutic means available. In case of failure, we again use intubation. Two American physicians, Litchfield and Hardman, and later Gover and Hardman, in 1923, introduced the therapy in stenosis of the larynx with suction through a metal catheter under direct laryngoscopy.[10]

The diagnosis of laryngeal diphtheria is often complicated with several difficulties, but this condition should be distinguished from Chevalier Jackson's disease,[12] acute laryngotracheobronchitis. The latter disease has been studied by the French laryngologists Le Mée and his colleagues and was reported on by them before the Congress of the French Society of Otorhinolaryngology in 1937; we intend to give our special attention to this subject in our next study.

Tracheotomy.—The practice of tracheotomy is quite old. In 1768, it was performed by the surgeon Louis,[13] under the name of bronchotomy, in the extraction of foreign bodies from the trachea. In 1786, another surgeon, J. P. Petit applied this method in treatment of a child with a foreign body in the trachea. Tracheotomy was performed under Bretonneau in 1825. We recur to it whenever intubation does not bring forth the expected result, that is, normal respiration, or when the tube is often ejected. Whenever after withdrawal of the

12. Rohmer, P.; Oberling, C., and Tulasne, R.: Rev. franç. de pédiat. **14**:283, 1938.

13. Mém. Acad. roy. de chir. **12**:201 and 349, 1768.

tube stenosis is produced owing to necrosis of the mucous membrane occasioned by the pressure of the tube, immediate intervention is necessary. The withdrawal of the tube from those who have undergone tracheotomy is usually done quite successfully and is done for all such patients on the fifth or sixth day. No doubt remains that successful treatment is due mainly to administration of penicillin in large doses, through which the eventuality of the complications of bronchopneumonia is prevented.

D. MORTALITY

Of a total of 551 patients with diphtheria, 32 died, an increase in mortality of 5.8 per cent.

TABLE 7.—*Deaths from Diphtheria According to Age Group*

Age	0 to 12 mo.	1 to 2 yr.	3 to 4 yr.	5 to 7 yr.
Deaths	14	12	5	1

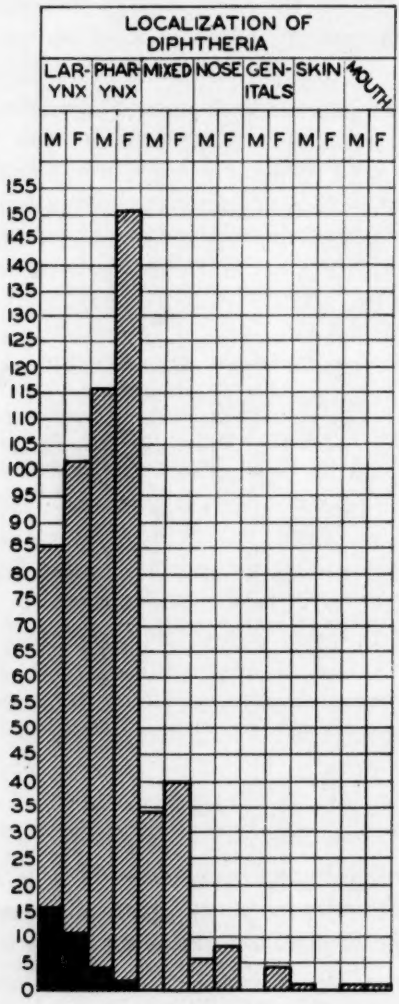
TABLE 8.—*Mortality in Diphtheria According to Type of Disease and After Tracheotomy*

Month	Laryngeal Diphtheria	Pharyngeal Diphtheria	Mixed Type	After Tracheotomy
April	1	2	..	..
May	..	..	..	..
June	..	..	..	..
July	..	..	..	1
August	..	..	..	..
September	..	..	..	2
October	3	..	..	..
November	2	1	..	..
December	5	1	..	4
January	6	1	..	..
February	3	1	..	..
March	..	..	..	..
Total	19	6	..	7

Mortality according to age is presented in table 7, according to sex and localization of the disease in the chart, and according to month of occurrence and type of disease in table 8.

Mortality is related to the day of illness as follows: The highest mortality rate was noted in patients admitted to the hospital on the third to the fourth day of illness, that is, a total of 24 deaths. The remaining deaths were reported in persons admitted on the first, fifth and seventh days of disease. Analysis according to age follows: Of 9 patients admitted on the third day of the disease who died, 6 belong to the group 0 to 12 months of age and the 3 others to the group 1 to 2 years old. Of those who died on the fourth day of dis-

ease, amounting to 15, 2 were from 0 to 12 months, 6, from 1 to 2 years old and 3, from 3 to 4 years old. On the fifth day of disease, 2 from those 2 to 12 months old and 2 between 1 and 2 years of age died. Two deaths on the seventh day of illness occurred in children 4 years old; finally, 1 child, 7 years of age, died on the second day of illness.



Graph showing total deaths due to diphtheria according to localization and sex.

The number of patients in relation to sex and localization of the disease and their connection with mortality are shown in table 3. In this table the number of girls exceeds that of boys by 63, that is, 244 boys, and 307 girls. Most of these deaths are due to laryngeal diphtheria. Thus, of 262 patients, 26 died, a rate of 9.9 per cent, while

in the remaining 362 patients with various forms of the disease only 6 mortalities are recorded, a rate of 2 per cent. Of the patients with laryngeal diphtheria shown in table 2, 66 patients underwent the intubation process and 25 tracheotomy. Of these, 16 were boys and 9 girls, their ages being as follows:

Age						
0 to 12 Mo.		1 to 2 Yr.		2 to 4 Yr.		
Boys	Girls	Boys	Girls	Boys	Girls	Total
3	1	8	6	4	3	25

In regard to mortality the figures are as follows: Of 25 patients on whom tracheotomy was performed, 7 died, a mortality rate of 28 per cent. In 41 others who underwent intubation only, 11 died, a mortality of 25 per cent (table 9).

TABLE 9.—*Tracheotomies, According to Month of Performance and Number of Deaths*

Month	No. of Patients	No. of Deaths
July	2	1
September	5	2
December	13	4
January	5	..
Total	25	7

Table 9 shows that the greatest number of tracheotomies were performed in December. A total of 9.1 per cent of patients with laryngeal diphtheria underwent tracheotomy.

The cause of death for each patient was as follows: Three died probably because of delay of tracheotomy, which followed repeated intubations. One died in spite of timely tracheotomy because the illness had been neglected. The other 3 died from the myocarditis which followed. The 10 deaths among the 41 patients who were submitted to intubation were probably due to the following reasons: Seven deaths after repeated intubations were caused by myocarditis, the other 3 by both bronchopneumonia and myocarditis. The remaining 17 deaths were due to bronchopneumonia and myocarditis in 8 cases and to myocarditis in 9.

CONCLUSIONS

We considered it of interest to give a description of the epidemic of diphtheria which occurred in Athens during the winter 1946-1947, because it was the most important one known to the Children's Hospital from the time of its establishment.

In one year only, and specifically during the winter months, 551 patients with diphtheria were treated in the hospital, that is to say,

approximately one fifth of the total number of patients with diphtheria treated since its foundation. Thus, the opportunity was given to the hospital once more to study the problem of the therapy in this disease.

1. The therapy applied was based chiefly on the belief always held in our hospital, that large doses of serum should be used. Such doses were given on a large scale in combination with penicillin. The results were absolutely satisfactory. Of 551 patients, we lost 34. Thus, our statistical record may be compared with the best in the international literature. According to our expectation, the curve of the epidemic of diphtheria continued at the same level during the winter 1947-1948, with 533 cases, of which 24 were fatal. From March 1948 to February 1949, the number of cases in an epidemic has been subsiding. Thus, we had only 381 cases of diphtheria, 10 of which were fatal.

2. From our present observations, the action of penicillin should be studied mainly in the prophylaxis and the therapy of complications which are often fatal consequent to intubation and which oftener follow tracheotomy. Presumably, penicillin may also have a specific reaction. We must pay tribute to penicillin for the obvious improvement noted in children who underwent tracheotomy. (Of 25 children treated by tracheotomy, 7 died.) Because infection in tracheotomy, precisely the complication most feared in clinics of older times, is now limited to such a great extent, probably the clinic of today would consider it a risk to the infant's life to postpone intubation.

3. In the hospital we have further investigated the period diphtheria bacilli are carried by the patient. Our conjectures on this subject will constitute a special treatise after our research on therapy. We wish to draw attention to the fact that the pediatrician is compelled to go to the uttermost limit in order to evade intubation, and for this reason, in spite of the relatively large number of patients with laryngeal diphtheria (262), only a small number (66) underwent intubation. We succeeded in this through intense antitoxin treatment, in conjunction with the other means we apply for such patients. From our present research, the importance of the day on which antitoxin treatment is started is plainly proved. The patient's chances are exceptionally poor when therapy is not started as soon as possible. The number of deaths occurring when therapy was begun on the fourth day was exactly fourfold.

4. The present study confirms the importance of the preventive antidiphtheria vaccination. Of 551 patients, only 4 were ascertained to be vaccinated and for all 4 the outcome was favorable.

5. The hospital is under the impression that among the various serums Pasteur serum is superior, and that among the new ones of the predominantly condensed type it was proved that the American serum causes a more intense reaction and a more advanced appearance of

immunity. Although serums were widely used, there were no accidents reported, even with intravenous administration.

6. Because the intensity of the epidemic during the last year does not prove that we have reached its peak and we cannot eliminate the possibility of a still greater extent of the disease next year, it is wise to recommend preventive vaccination at an early date. It is, of course, understood that, owing to the widespread incidence of tuberculosis among us, application of vaccination on a large scale should not depart from indications and counterindications for it, as dictated by the individual circumstances of the patient.

7. Ouabain U.S.P. has been widely used for the control of the myocarditis due to diphtheria. In the patients with severe conditions we administered it intravenously and in doses stronger than for the adults. We administered 0.125 mg. in two doses daily. The same dose has been given for four to five days. In many patients we observed signs of lowered resistance of the myocardium with peripheral collapse of the vessels, hardening of the liver, vomiting and tachypnea. Ouabain has also been administered orally in place of digitoxin U.S.P. (digitaline nativelle®). We think that the use of ouabain has given good results. We administered doses of 0.33 mg. daily for many days without harmful reactions.

St. Sophie's Children's Hospital, Pediatric Clinic of Athens University.

RESULTS OF SCHICK TESTING THREE YEARS AFTER THE INJECTION OF PROTAMINE DIPHTHERIA TOXOID

VICTOR ROSS, Ph.D.
NEW YORK

THE RESULTS of antitoxin titrations of the blood of children who were immunized with protamine diphtheria toxoid [1] have previously been published. These data showed that children receiving either one or two doses had somewhat higher and more lasting levels of antitoxin than those reported following the use of equivalent quantities (Lf unit) [2] of alum-precipitated toxoid.[3] Between eleven and eighteen months after one injection of protamine toxoid (20 to 25 Lf units), 30 per cent of the children had 1/10 unit or more of antitoxin per cubic centimeter of serum. Between nine and fifteen months after two doses, 90 per cent had 1/10 unit or more and 58 per cent had 1/5 unit or more.

Since bleedings were impracticable owing to the objection of the mothers, it was decided to obtain a measure of the duration of the immunity by means of the Schick test. This is admittedly but a partially quantitative test and gives information regarding only the minimal level of antitoxin present. It is generally agreed, however, that a negative reaction to the Schick test is presumptive evidence of immunity to diphtheria, or at least of a state in which, in the event of infection, a more rapid increase in production of antitoxin takes place than with a positive reaction to the test. Consequently, there is a much better chance of survival. Earlier,[4] it was observed that the initially positive reaction in 95 per cent of the children who received one dose of prota-

From the Department of Biochemistry, College of Physicians and Surgeons, Columbia University.

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1. Ross, V.; Clapp, F. L., and Schimpf, B. W.: Antitoxin Titers Following Immunization with Protamine-Precipitated Diphtheria Toxoid, Am. J. Pub. Health **36**:645-649, 1946.

2. The Lf unit is that amount of toxoid (or toxin) which flocculates most rapidly with 1 unit of antitoxin in a series of mixtures containing constant amounts of toxoid (or toxin) and varying amounts of antitoxin.

3. Volk, V. K., and Bunney, W. E.: Diphtheria Immunization with Fluid Toxoid and Alum-Precipitated Toxoid, Am. J. Pub. Health **32**:690-699, 1942.

4. Ross, V.: Preparation and Immunizing Properties of Protamine-Diphtheria Toxoid, Am. J. Dis. Child. **68**:172-181 (Sept.) 1944.

mine toxoid became negative in two to two and one-half months and that this figure rose slightly at six months. The reaction of almost every child who was given two doses (25 Lf units each) was converted from positive to negative.

The Schick test, with controls, has recently been performed on 121 children thirty-six to thirty-eight months after they had received a single injection of protamine toxoid. (A few of them were tested at thirty-four or thirty-nine months.) All of them had positive reactions to the Schick test before they received the toxoid, and they had not been tested in the interval. The ages of 98 of the children at the time of the second test ranged from 42 months to 5 years; the rest were between 68 months and 12 years old.

RESULTS

In 9 children the result was read four days after the injection of the Schick toxin and again three days later. No change in the four day reading occurred, with the exception of one result which was doubtful on the fourth day and positive on the seventh. Thirty-two were seen seven days after, 77 were seen six days after, and 1 each on the second, tenth and eleventh days after, the injection. Of the 121 children, the reaction of 6 to the Schick test were positive and the reaction of 1 was pseudopositive. Therefore, approximately 95 per cent were, presumably, still immune. The ages of the children with positive reactions at the time of the test were 42, 44, 46, 53, 95 and 125 months. It is of interest that all 6 positive reactors were among those subjects, the total number of whom was 58, tested in the months of October, November and February, while among the 63 tested in the months of April and June there were none with positive reactions.

Dudley, May and O'Flynn [5] observed that relapses in persons showing immunity on the Schick test among a naturally immunized population occurred in the early part of the winter (November and December) before the immunizing forces which take effect in the winter have had sufficient time to make themselves felt. They were of the opinion that these natural forces ran parallel to the seasonal incidence of infection with diphtheria in the institution in which they made their study.

In the present study, the artificially immunized children lived in their parents' homes; contact with actual cases of diphtheria was, probably, nil, while contact with carriers cannot be estimated. The fact that the percentage of children whose reactions were negative to the Schick

5. Dudley, S. F.; May, P. M., and O'Flynn, J. A.: Active Immunization Against Diphtheria: Its Effect on the Distribution of Antitoxic Immunity and Case and Carrier Infection, Special Report Series, no. 195, Medical Research Council, London, His Majesty's Stationery Office, 1934.

test after three years was the same as that previously observed in a different group several months after one injection suggests that the occurrence of the 6 positive reactors in the three months mentioned was simply due to chance. It may signify, further, that the initial antitoxin levels produced were sufficiently high in a large percentage of subjects, that few, if any, fell below the minimal level for a negative reaction to the Schick test after thirty-six months.

REPORTS IN THE LITERATURE ON RESULTS OF SCHICK TESTING

Many reports exist in the literature dealing with the results of Schick testing at intervals following immunization. The lack of data regarding the actual quantity (number of Lf units) injected often makes interpretation difficult. Duke and Stott [6] reported that two years after the injection of alum-precipitated toxoid the reactions of 4 per cent of 354 children were positive and that after three years those of 12 per cent were positive. Nevius and McGrath [7] observed that 100 per cent of the children to whom they gave injections of alum-precipitated toxoid had negative reactions to the Schick test after twelve months and that 80 per cent had negative reactions after five years. Dean and Hyman,[8] using one dose of alum-precipitated toxoid which met the requirements of the National Institute of Health, recorded that among a group of children under 10 years of age, 92 per cent were negative reactors at four months, 93 per cent at sixteen months and 95 per cent at twenty-eight months. For all children up to 15 years of age, the percentages were 86, 87 and 89, respectively. These figures are probably somewhat high, owing to the fact that many of the children had received the stimulus of one or two intervening Schick tests. Bundesen, Fishbein and White [9] reported that among 119 children between the ages of 5 and 7 years who were given one dose of alum-precipitated toxoid in 1934, the reactions of 6 were positive in 1936.

These examples are cited simply to give some idea of the results obtained with one dose of alum-precipitated toxoid and not for the purpose of comparing this form of toxoid with protamine toxoid, for Schick tests are not entirely suitable for comparing the efficacy of various forms

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6. Duke, H. L., and Stott, W. B.: Duration of Artificial Active Immunity Against Diphtheria, Brit. M. J. **2**:710-711 (Dec. 4) 1943.

7. Nevius, W. B., and McGrath, A. C.: Duration of Immunity to Diphtheria Achieved by Toxin-Antitoxin and Alum-Precipitated Toxoid, Am. J. Dis. Child. **59**:1266-1270 (June) 1940.

8. Dean, A. S., and Hyman, S.: Alum-Precipitated Toxoid for the Prevention of Diphtheria, Am. J. Pub. Health, **28**:1170-1174, 1938.

9. Bundesen, H. N.; Fishbein, W. I., and White, J. L.: Diphtheria Immunity in Chicago, J. A. M. A. **112**:1919-1923 (May 13) 1939.

of diphtheria toxoid. Quantitative determinations of antitoxin [10] are to be preferred when conditions permit taking samples of blood. When they do not, Schick tests are still of value, since it is to be expected that it will take longer for a group of initially higher titers to fall below the minimal level for a negative reaction to the Schick test than for a group of initially low ones. Schick tests done at intervals, but only once on each child, may still serve as a guide, though not the most quantitative one, to the immunizing efficacy of a given preparation.

In spite of the satisfactory immune status of these subjects, it is recommended that two doses of protamine toxoid should be administered rather than one. This belief is based on the considerably larger percentage of children who produce greater amounts of antitoxin (1/10 unit or more) after two injections. Thus, protection will be more prolonged in a greater proportion of children.

SUMMARY

The results of the Schick test performed, with controls, on 121 children thirty-six to thirty-eight months after they received a single injection of protamine diphtheria toxoid are reported. Literature on the results of Schick testing at intervals following immunization is briefly reviewed. In order to prolong protection, the administration of two doses of protamine diphtheria toxoid, rather than one, is recommended.

Dr. Samuel R. Berenberg, Dr. Bluma Lipshitz and Dr. Paul F. de Gara assisted in this investigation. The Department of Health of the City of New York and the New York Diet Kitchen Association provided facilities for the work, and the former supplied the Schick toxin materials.

630 West One Hundred and Sixty-Eighth Street (32).

10. Fraser, D. F., and Halpern, K. C.: A Comparison of One Dose of Alum-Precipitated with Three Doses of Unmodified Toxoid, Canad. Pub. Health J. **26**:469-475, 1935. Ross, Clapp and Schimpf.[1] Volk and Bunney.[3] Bundesen, Fishbein and White.[9]

Case Reports

PROTEUS VULGARIS MENINGITIS

MARTIN Z. KAPLAN, M.D.
AND
ALVIN C. POWELEIT, M.D.
LOUISVILLE, KY.

MENINGITIS caused by Proteus vulgaris (Bacillus proteus) is rarely reported, but those few cases found in the literature have a striking resemblance. Our patient, who was treated at the Louisville General Hospital during December 1946 and January 1947, is being reported on with the purpose of reviewing the literature, as well as discussing the value of the newer antibiotic substances. The last case, reported by Myers [1] in 1944, was the tenth up to that time.

Kernan,[2] in 1922, reported on 2 patients with P. vulgaris meningitis with thrombosis of the lateral sinus, jugular vein and cavernous sinus following chronic otitis media and peritonsillar abscess. Both patients died.

McGovern,[3] in 1936, reported on 2 patients with the complication of lateral sinus thrombosis following chronic otitis media. These patients also died.

Gerzog [4] reviewed the literature up to 1939 when he reported on his patient, who was treated with bacteriophage and recovered. One other recovery in this group was that of Stein's patient [5] in 1930. Mastoiditis and meningitis developed in this patient following tonsillectomy for a malignant growth. P. vulgaris was cultured locally but not in the blood. The patient was not described as severely ill.

From the Department of Pediatrics and the Eye, Ear, Nose and Throat Department, University of Louisville Medical School (Dr. Kaplan).

1. Myers, E. L.: Otitic Meningitis Due to Bacillus Proteus, Jugular Sinus Thrombosis, Septicemia Due to Streptococcus Viridans, Thoracic and Cardiac Complications: Recovery, Laryngoscope **54**:619 (Nov.) 1944.

2. Kernan, J. D., Jr.: Two Cases of Infection by Bacillus Proteus; Laryngoscope **32**:304 (April) 1922.

3. McGovern, F. H.: Fatal Otogenic Infection with Bacillus Proteus: Report of Two Cases, Arch. Otolaryng. **24**:618 (Nov.) 1936.

4. Gerzog, B. G.: Bacillus Proteus in Otogenic Infections, Secondary Mastoiditis, Thrombosis of the Lateral Sinus and Bacteremia, Arch. Otolaryng. **30**:275 (Aug.) 1939.

5. Stein, S.: Bacillus Proteus Vulgaris Infection in Secondary Mastoiditis Following Tonsillectomy, and in Radium Implantation in Tonsils, Ann. Otol., Rhin. & Laryng. **39**:1155 (Dec.) 1930.

The other patients reported on [6] gave a history of chronic otitis media followed by meningitis. In almost everyone who was treated surgically or examined post mortem, the lateral sinus and internal jugular vein were obliterated by thrombosis. In all those who died, the blood cultures were positive for the organism.

In the patient reported on by Myers,[1] the meningitis followed chronic suppurative otitis media. At operation, the lateral sinus and the jugular vein were thrombosed. The patient also had Streptococcus viridans septicemia, and thoracic and cardiac complications developed. However, after extensive surgical therapy and the use of sulfapyrazine and sulfadiazine, the patient recovered. In this patient, as in ours, on the first reports the proteus organisms in the spinal fluid were considered contaminants.

In the patient being reported on, vulgaris meningitis also followed chronic otitis media and was accompanied with many complications.

REPORT OF CASE

D. G., a 9 year old white girl, was admitted to the Louisville General Hospital Dec. 18, 1946 with the chief complaint of stiffness of the neck for the past five days. Since 1941, after she had scarlet fever with complicating otitis media, she had had recurrent infections of the middle ear (left). Nine days prior to her admission, she began to complain of soreness in her left ear, and on the following day, the ear started to drain purulent material. She became listless after this and complained of pain in her left jaw that was thought to be due to an infected tooth. At this time her neck became somewhat stiff. Her private physician treated her with sulfadiazine, but after eleven doses she started vomiting and the drug was discontinued. Her appetite waned; she became more listless; her neck became stiffer, and a severe headache developed. After her temperature started spiking, her parents brought her into the hospital. The previous history and family history, other than what has been given, were noncontributory.

Physical examination revealed an asthenic, well nourished white girl about 9 years of age, appearing acutely ill and quite apprehensive, although cooperative. Her temperature was 104 F. (rectum); respirations numbered 26 and the pulse rate was 88. The skin was hot and dry. No petechiae were observed. The pupils were equal and regular and reacted to light. The extraocular muscles were normal. The fundi revealed decided papilledema. The right ear drum was reddened. The left aural canal was so edematous that the drum was not visualized; however, no discharge was noted. There was no tenderness over either mastoid bone The anterior and posterior cervical glands were enlarged and tender. There were no infected teeth. The pharynx was mildly injected. The neck was stiff and rigid. The lungs, heart and abdomen showed no abnormalities. Neurologic examination revealed the presence of the Kernig and Brudzinski signs.

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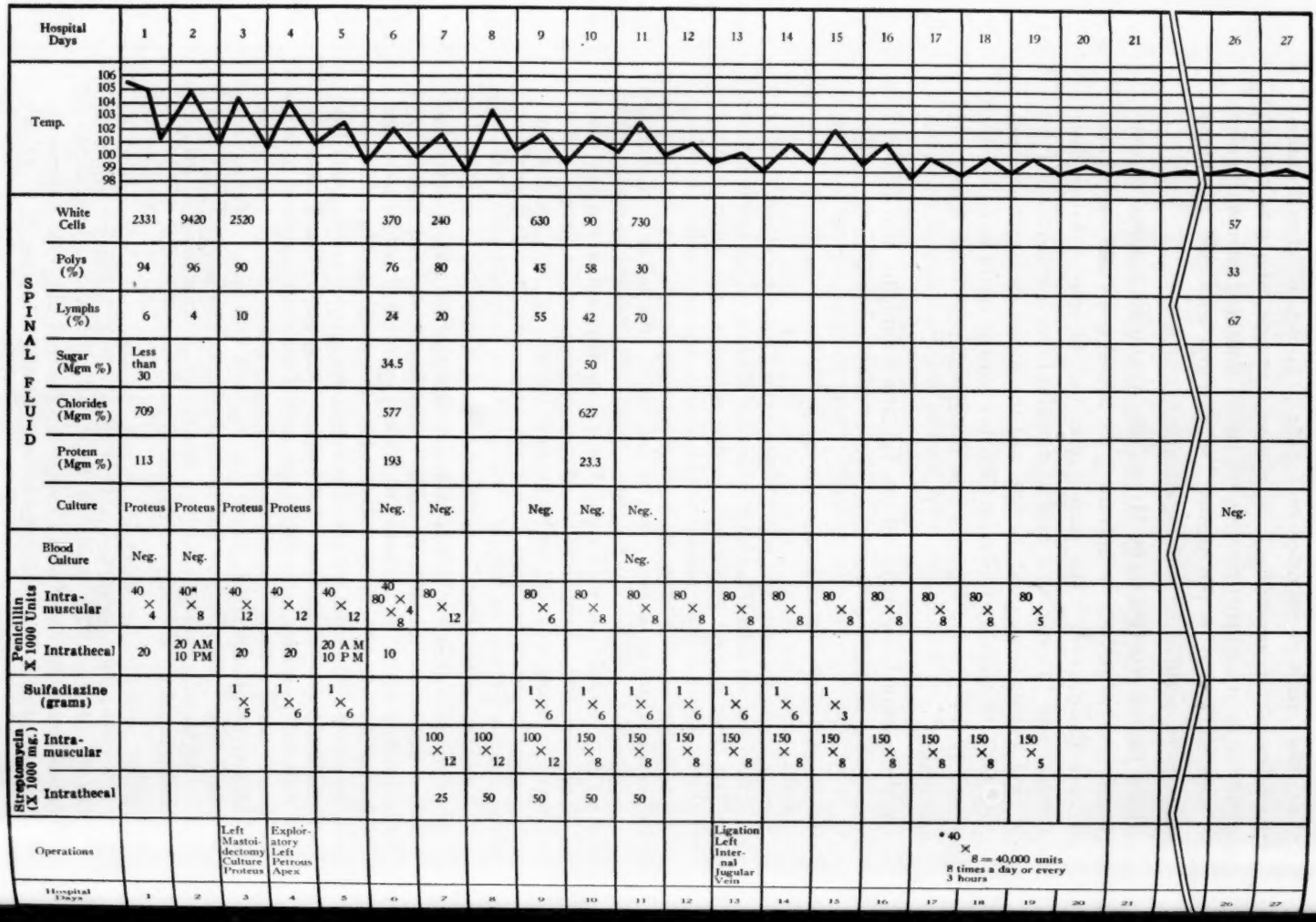
6. Neal, J. B., and Abramson, H.: The Genus Proteus in Meningitis, Am. J. M. Sc. **174**:665 (Nov.) 1927. Smith, A. B. P., and Miller, S.: Lateral Sinus Thrombosis Due to Bacillus Proteus, Lancet **1**:862 (April 13) 1935. Kortenhaus, F.: Otitic Meningitis Due to Bacillus Proteus, Ztschr. f. Laryng., Rhin. **19**:146 (Jan.) 1930.


Hospital Days
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 26 27
Temp.
106 105 104 103 102 101 100 99 98
SPINAL FLUID
White Cells
2331 9420 2520 370 240 630 90 730 57
Polys (%)
94 96 90 76 80 45 58 30 33
Lymphs (%)
6 4 10 24 20 55 42 70 67
Sugar (Mgm %)
Less than 30
34.5 50
Chlorides (Mgm %)
709 577 627
Protein (Mgm %)
113 193 23.3
Culture
Proteus Proteus Proteus Proteus Neg. Neg. Neg. Neg. Neg. Neg. Neg.
Blood Culture
Neg. Neg. Neg.
Penicillin X 1000 Units
Intramuscular
40 × 4
40* × 8
40 × 12
40 × 12
40 × 12
40 80 × 4 × 8
80 × 12
80 × 6
80 × 8
80 × 8
80 × 8
80 × 8
80 × 8
80 × 8
80 × 8
80 × 8
80 × 8
80 × 8
80 × 5
Intrathecal
20
20 AM 10 PM
20
20
20 AM 10 PM
10
Sulfadiazine (grams)
1 × 5
1 × 6
1 × 6
1 × 6
1 × 6
1 × 6
1 × 6
1 × 6
1 × 6
1 × 3
Streptomycin (X 1000 mg.)
Intramuscular
100 × 12
100 × 12
100 × 12
150 × 8
150 × 8
150 × 8
150 × 8
150 × 8
150 × 8
150 × 8
150 × 8
150 × 8
150 × 8
150 × 5
Intrathecal
25
50
50
50
50
Operations
Left Mastoidectomy Culture Proteus
Exploratory Left Petrous Apex
Ligation Left Internal Jugular Vein
* 40 × 8 = 40,000 units 8 times a day or every 3 hours
Hospital Days
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 26 27

The spinal fluid was under 550 mm. of water pressure and appeared xanthochromic and cloudy. The white cell count was 2,330 with 96 per cent polymorphonuclear cells. A primary smear was read by the resident physician as a gram-positive diplococcus. A blood count showed 4,500,000 red cells, with 14.5 Gm. of hemoglobin. The white blood cell count was 17,000, with 86 per cent polymorphonuclear cells and 14 per cent lymphocytes. The urine was normal.

Our initial impression was that of pneumococcic meningitis secondary to mastoiditis. Administration of penicillin was started immediately; 20,000 units was given intrathecally twice a day and 40,000 units intramuscularly every three hours. Sulfadiazine was withheld because of the patient's history of intolerance. It was decided to observe the effect of this medication for twenty-four to thirty-six hours before giving any surgical treatment. At the end of this time no clinical improvement was noted, and the temperature was spiking to 104 F. (rectum). It was also noted at this time that paralysis of the left facial and left abducens nerves (Gradenigo's syndrome) had developed.

A simple mastoidectomy (left) was done that evening. As the periosteum over the mastoid process was retracted, two perforations were seen which exuded pus. The anterior perforation was entered with a "V" gouge. A small cholesteatoma and two abscesses, more or less encapsulated, were seen along the external wall of the canal and sinus. Necrotic cells and pus were curetted away, and the lateral sinus was exposed. A thrombus was found in the lateral sinus which was thought to extend to the jugular bulb. During the manipulation bleeding began above the thrombus (in the lateral sinus) and was controlled with packs. Owing to the patient's condition, it was decided to close the incision and wait for a more favorable time to explore. Cultures were taken of the purulent material.

After the operation, administration of sulfadiazine was started, together with the penicillin. The child's condition the next evening was improved, and it was decided to explore the petrous pyramid. This time the incision was opened and extended upward. A modified form of the Eagleton operation was used to reach the petrous apex. The apex was curetted clean and the cavity packed and closed. The child was returned to the ward in fair condition.

The initial culture of spinal fluid was reported to be positive for P. vulgaris, as was the culture taken on the second day. Unfortunately, both growths were considered contaminants, and not until we received reports on four different spinal fluid cultures and the mastoid culture as positive for P. vulgaris did we consider it the infecting organism. We felt that a pneumococcic organism was present also, but that the P. vulgaris overgrew it. Repeated cultures of the blood were negative for pathogenic organisms.

Since the child was not doing well on her medicaments, it was decided to use streptomycin in their place. The dosage was 25,000 units per pound (0.5 Kg.) of body weight per day, 100,000 units every two hours intramuscularly; 50,000 units of streptomycin were given intrathecally daily. For the next two days no improvement was noted; in fact, the temperature became so elevated that penicillin and sulfadiazine were introduced again.

Eleven days after her admission and seven days after the operation, the temperature was spiking daily to 103 to 104 F. (rectum), and the spinal fluid remained cloudy. The spinal fluid sugar showed an increase. The paralysis of the facial and abducens nerves persisted. It was felt that the thrombus of the left internal jugular vein was responsible for the temperature spike; so on December 30 the vein was ligated. Within two days her temperature returned to normal; she became much

more alert and responsive. The left ear was dry and the paralysis of the facial and abducens nerves displayed pronounced improvement.

Five days after the ligation, sulfadiazine was discontinued, and four days later the use of penicillin and streptomycin was stopped. Within forty-eight hours after discontinuation of all medication, she became drowsy. Seventy-two hours later she vomited, but it was not until five days after the discontinuation of all medication that she complained of severe occipital headaches. At this time she was vomiting oftener and was more lethargic and listless.

Physical examination revealed the temperature to be 98.2F.; respirations were 24 per minute and the pulse rate 58. The blood pressure was 160 systolic and 84 diastolic. A healed mastoidectomy scar (left) and impairment of hearing on the left side were noted. The pupils were dilated but reacted to light. Severe bilateral papilledema, mild paralysis of the left abducens nerve and complete recovery of the left facial nerve were observed. The visual fields showed some constriction; moderate stiffness of the neck was still evident. The deep reflexes were normal. In the Romberg sign there was swaying to the left. The Babinski sign was present bilaterally. There was no ankle clonus or past pointing. A spinal fluid examination revealed a pressure of 450 mm. of water with a normal reaction to the Queckenstedt test. Globulin showed a 2 plus precipitation, with 57 lymphocytes and 19 polymorphonuclear cells. The neurologists felt that this increased intracranial pressure was caused by interference in venous return due to the thrombosis and the ligation of the internal jugular vein. Abscess of the brain was ruled out because of the afebrile state and lack of localization of the findings. It was decided to observe the patient.

In the following ten days the symptoms of increased intracranial pressure subsided and the papilledema disappeared.

For a few weeks the child experienced some difficulty in walking and had to be helped from time to time. When seen in the clinic June 15, 1947, she could walk normally; her left eye had recovered from its paralysis, and she was able to hear normal conversation with her left ear. Neurologic examination at the time elicited no abnormalities. The papilledema had disappeared. The patient was considered to have recovered completely.

CONCLUSION

P. vulgaris meningitis is a complication of a chronic form of suppurative otitis media and mastoiditis. When patients with this condition are operated on, one almost invariably observes thrombosis of the lateral sinus and internal jugular vein. P. vulgaris in spinal fluid cultures is generally considered a contaminant, and not the causative organism, until repeated cultures consistently show its presence. We feel that another organism is apt to be present which may account for the acute flare-up and that on culture P. vulgaris outgrows the secondary organism. In our case it is felt that a pneumococcus may have been present, but it was not seen on culture because P. vulgaris crowded it out.

The value of streptomycin in P. vulgaris meningitis was not impressive, and after forty-eight hours we resumed the administration of

penicillin and sulfadiazine because of the rise in temperature and the general appearance of the patient. We did continue with streptomycin because it was felt that heroic measures were needed. The spinal fluid cultures were negative for pathogenic organisms before use of streptomycin was started, but we did not know that at the time, since it takes thirty-six to forty-eight hours for reports on our spinal fluid cultures.

The complication of the increased intracranial pressure following ligation of the internal jugular vein is most interesting and was not described for any of the other 4 patients with meningitis on whom similar operations were performed.

SUMMARY

A patient with Proteus vulgaris meningitis with many complications and final recovery is reported on.

840 Barret Avenue.

THROMBOENDARTERITIS WITH MULTIPLE MYCOTIC ANEURYSMS OF BRANCHES OF THE PULMONARY ARTERY

CONRAD L. PIRANI, M.D.
FRED E. EWART Jr., M.D.
AND
AUDREY L. WILSON, M.D.
CHICAGO

ANEURYSMS of the trunk and of the primary branches of the pulmonary artery are a rare entity. According to recent reviews on large numbers of cases,[1] etiologic factors, in order of frequency, are congenital defects, syphilis, arteriosclerosis, rheumatic fever, bacterial endocarditis or endoarteritis and trauma.

Aneurysms of the smaller branches of the pulmonary arteries are found frequently in tuberculous cavities and occasionally in other chronic infectious cavities of the lungs.[2] In such cases, however, they are small, rarely reaching a size above a few millimeters in diameter. Larger intrapulmonary aneurysms, associated either with an intrinsic disease or with a congenital defect of the arterial wall, are rare.

Syphilis has occasionally been found to tbe the etiologic factor in large aneurysms.[3] Congenital defects, such as patent ductus arteriosus and patent interatrial or interventricular septum, are occasionally accompanied with pronounced ectasia of the pulmonary artery and its branches, and more rarely by saccular aneurysms within the lungs. In such cases the increased blood pressure within the pulmonary arteries, because of the abnormal communication between the general and the pulmonary circulation, plays an important role. Infected (mycotic) embolism was considered responsible in a number of instances in which aneurysms of the pulmonary arteries were found associated with bac-

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From the Departments of Pathology, Pediatrics and Roentgenology of the University of Illinois College of Medicine.

1. Boyd, L. J.: Aneurysms of the Trunk and Main Branches of the Pulmonary Arteries: Analysis of One Hundred and Fifty-Two Cases, Mod. Conc. Cardiovasc. Dis., 1941, vol. 10, no. 2. Deterling, R. A., and Clagett, O. T.: Aneursyms of the Pulmonary Artery: Review of the Literature and Report of a Case, Am. Heart J. **34**:471, 1947.

2. Karsner, H. T.: Human Pathology, ed. 6, Philadelphia, J. B. Lippincott Company, 1942, p. 475.

3. Warthin, A. S.: Syphilis of the Pulmonary Artery, Am. J. Syph. **1**:693, 1917.

terial endocarditis of the pulmonary artery and of the ductus arteriosus. In cases of patent ductus arteriosus, bacterial endocarditis of the aortic valve, and less frequently of the mitral valve, was the source of the mycotic emboli. In a few reported instances it was assumed that congenital aneurysms became secondarily infected. However, it was impossible to determine whether the primary cause of the aneurysms was a congenital defect or an inflammatory disease of the arterial wall.[4]

We wish to report an additional case of multiple mycotic aneurysm of the branches of the pulmonary arteries within the lungs. This case was unusual because no congenital defect could be demonstrated and because the aneurysms were on the basis of emboli originating from chronic thrombophlebitis of the veins of the legs and of the inferior vena cava.

REPORT OF CASE

History.—The patient, a 10 year old Greek boy, began to experience occipital headaches and cough. The cough subsided in two weeks, but the headaches became progressively severer, and his visual acuity deteriorated. Three and one-half

4. Thompson, H.: Multiple Aneurysms in the Heart, Lungs and Cavity of the Cranium, M. Times & Gaz. **2**:56, 1877. Duffield, J. F.: Aneurisms of the Right and Left Pulmonary Arteries: Pulmonary Insufficiency; Dilatation of the Right Ventricle, Am. J. M. Sc. **83**:77, 1882. Sachs, R.: Zur Casuistik der Gefässerkrankungen, Deutsche med. Wchnschr. **18**:433, 1892. Kidd, P.: Embolic Aneurysm of the Pulmonary Artery, Tr. Path. Soc. London **44**:47, 1892-1893. Loveland, B. C.: Aneurysm of the Pulmonary Artery, with Report of a Case, M. Rec. **59**:349, 1901. Krzyszkowski, J.: Aneurysma des Stammes der Pulmonararterie und multiple Aneurysmen ihrer Verästelungen bei Persistenz des Ductus Botalli, Wien. klin. Wchnschr. **15**:92, 1902. Henschen, S. E.: Das Aneurysma arteriæ pulmonalis, Samml. klin. Vortr., 1906, no. 422-423 (Inn. Med. no. 126-127, p. 595). Trevor, R. S.: A Case of Multiple Mycotic Aneurysms of the Branches of the Pulmonary Artery Within the Lung, Proc. Roy. Soc. Med. (Path. Sect.) **5**:155, 1911-1912. Humphrey, Y.: Multiple Embolic Aneurysms of the Pulmonary Artery, J. Path. & Bact. **17**:212, 1912-1913. Wilkens, G. D.: Ein Fall von multiplen Pulmonalisaneurysmen, Beitr. z. Klin. d. Tuberk. **38**:1, 1917. Jores, L., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2, p. 757. Sherman, D. H., and Roman, B.: A Case of Multiple Aneurysms of the Branches of the Pulmonary Artery, Bull. Buffalo Gen. Hosp. **4**:39, 1926. Steinberg, W.: Zur Kenntnis des mykotischen Aneurysmas der Lungenschlagader, Virchows Arch. f. path. Anat. **290**:432, 1933. Brenner, O.: Pathology of the Vessels of the Pulmonary Circulation, Arch. Int. Med. **56**:1189 (Dec.) 1935. Palmer, H. D., and Kempf, M.: Streptococcus Viridans Bacteremia Following Extraction of Teeth: Case of Multiple Mycotic Aneurysms in Pulmonary Arteries; Report of Cases and Necropsies, J. A. M. A. **113**:1788 (Nov. 11) 1939. Höra, I., and Wendt, H.: Thromboendarteriitis der Lungenschlagader mit multiplen, mykotischen Aneurysmen, Wien. Arch. f. inn. Med. **35**:249, 1941. Lelli, G.: Multiple mykotische Aneurysmen der Lungenarterien bei ulzerösen Endokarditis der Aortenklappen und offenem Ductus Botalli, Zentralbl. f. allg. path. u. path. Anat. **77**:342, 1941.

months after the onset (Nov. 16, 1941) of these symptoms, he was admitted to the Research and Educational Hospital of the University of Illinois, where physical examination revealed nothing of significance except for the neurologic signs. In addition to the great loss of visual acuity, he had severe papilledema bilaterally. There was neither ventricular enlargement nor distortion. A diagnosis of encephalitis of unknown cause was made, and right subtemporal decompression was done to save his vision. He was discharged with considerable visual improvement, but with residual papilledema.

He was admitted again in December 1941 and in June 1942 with complaints of persistent tension in the area of the subtemporal decompression and of daily headaches. There was, however, considerable improvement in visual acuity. Lumbar punctures and a combined encephalogram and ventriculogram failed to yield any additional information as to the cause of his condition. No roentgenograms of the chest were taken during the third period of hospitalization, but a fluoroscopic examination demonstrated that the heart and lungs were normal. He was discharged, as improved, on July 12, 1942.

His fourth, and final, admission was on Dec. 3, 1945, when he entered with the following complaints: For the previous nine months he had had a persistent productive cough, general malaise, easy fatigability, mild, and then severe, chills every two weeks and a loss in weight of 15 pounds (6.8 Kg.). For the previous three months he had had a daily spiking temperature (oral) of 101 F., three episodes of hemoptysis, of about 100 to 200 cc. each; venous dilatation on the anterior body wall, and, for the previous month, intermittent swelling of his left ankle and knee. A roentgenogram of the chest two months before admission, taken at another hospital,[5] showed only an increase of bronchovascular markings in both pulmonary fields, but no evidence of parenchymal infiltration (fig. 1 *A*).

Physical Examination.—The boy had marked pallor, appeared chronically ill and weak, though apparently well nourished and had a hacking cough productive of blood-streaked sputum. The temperature was 101 F., the pulse rate 120, the respiratory rate 30 per minute, and the arterial blood pressure 120 systolic and 70 diastolic. The area of subtemporal decompression was bulging but not under great pressure. Visual acuity had not diminished. The left disk still showed mild edema; the right disk, none. Transillumination of the sinuses was poor, and subsequent roentgenograms supported an impression of chronic sinusitis. There were no masses in the neck, and no adenopathy was detectable until late in his stay in the hospital. Pulmonary resonance and breath sounds seemed remarkably good in the presence of voluminous expectoration, although rales could be heard posteriorly after an episode of hemoptysis. Dilatation of the superficial veins of the anterior body wall was prominent; the direction of flow was upward. The skin around these veins frequently showed areas of erythema, and there was a cordlike feeling on palpation, suggestive of thrombophlebitis. The liver was palpable 2 fingerbreadths below the costal margin. No masses were palpable within the abdominal cavity. There was no significant difference in the size of his extremities. The results of the neurologic examination were entirely normal.

Laboratory Data.—The hemoglobin measured 9.6 Gm. per hundred cubic centimeters; the red cell count was 3,820,000 and the white cell count 10,500 per cubic millimeter, with a normal differential count. Numerous cultures of the blood taken at the height of the patient's chills and fever were sterile. The Wassermann and Kahn tests gave negative reactions. The icterus index was 6. Cholesterol of the

5. Dr. J. S. McDavid, of Oak Park, Ill., gave us permission to use this roentgenogram.

blood was 148 mg. per hundred cubic centimeters; glucose, 100 Gm.; nonprotein nitrogen, 28 mg.; chlorides, 538 mg., and total proteins, 8.0 Gm., with a normal albumin-globulin ratio. Blood agglutination tests, including use of typhoid, paratyphoid, brucellosis and heterophil antibodies, all gave negative results. The urine was normal. Cultures of the sputum yielded staphylococci but no acid-fast organisms. The Mantoux test, as well as tests for coccidiosis, histoplasmosis and blastomycosis, gave negative results.

The dynamic pressure of the spinal fluid was normal; the culture was sterile; the gold curve was normal; serologic reactions were negative, and there were

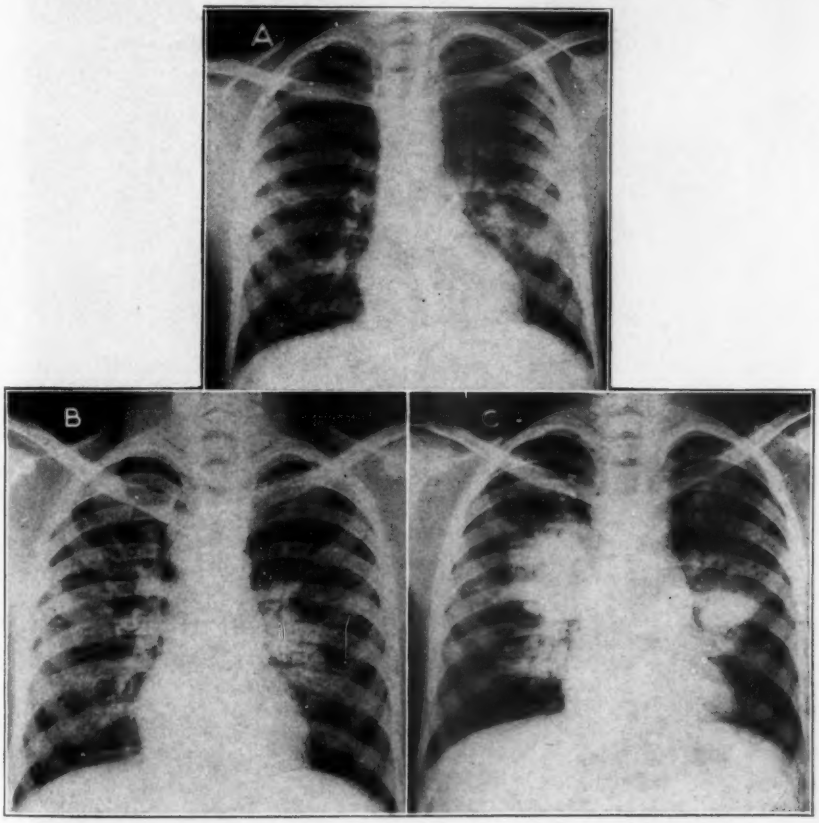

Fig. 1.—Roentgenograms of 10 year old boy. *A*, taken Oct. 10, 1945, shows a diffuse increase in bronchovascular markings but no parenchymal changes.

B, taken on Dec. 3, 1945, shows enlarged hilar nodes and conspicuous accentuation of bronchovascular markings. Small, irregular areas of density extend into the parenchyma of both pulmonary fields.

C, taken on Jan. 8, 1946, shows many round areas of density in the hilar regions and extending into the parenchyma. The edges of the areas of density are not discrete but blurred.

no cells. The bone marrow was entirely normal. The electrocardiogram was within normal limits. A roentgenogram of the chest taken on the patient's admission (fig. 1*B*) revealed enlarged hilar nodes and conspicuous accentuation of the bronchovascular markings radiating outward from both hilar regions, these

changes being more pronounced in the field of the left lung. Small, irregular densities extended into the fields of both lungs. These observations were interpreted as indicating a lymphogenous spread of a metastatic malignant growth. However, the possibility of lymphoma was also considered. A fluoroscopic examination of the chest gave no additional information concerning the parenchymal lesions. The cardiac outline and pulsations appeared normal. Examination of the esophagus with thick barium sulfate revealed no displacement by mediastinal

Fig. 2.—Section through the inferior vena cava, showing pronounced fibrosis of the entire wall. The lumen (at right) is obliterated by fibrous connective tissue, which contains numerous lymphocytes and presents extensive recanalization.

nodes. An intravenous pyelogram seemed to indicate pressure of the superior portion of the right renal pelvis, but a retrograde pyelogram demonstrated a normal kidney-ureter-bladder tract.

Clinical Diagnosis and Treatment.—The clinical impression at this time was that of a block of the inferior vena cava caused by a tumor and secondary infection due to metastases into the lungs. On this basis, he was given roentgen therapy to the abdomen, with subsequent temporary reduction in the venous dilatation of the anterior body wall.

Course of Illness.—During his stay in the hospital, the patient had repeated attacks of hemoptysis, with loss of about 30 cc. on each occasion, and, because of this bronchoscopic examination was delayed until the condition had been quiescent for at least ten days. Bronchoscopic examination was finally attempted, but bleeding occurred immediately and no satisfactory examination could be carried out. A roentgenogram of the chest taken thirty-six days after his admission to the hospital (fig. 1*C*) showed considerable progression of the parenchymal lesions. Many large, rounded densities, which extended peripherally into the pulmonary fields, could be distinguished in the hilar regions. On the left side the nodules were not well demarcated, but on the right side rounded, homogeneous densities could be distinguished. The largest of these, lying adjacent to the ascending aorta, measured 5.5 by 6 cm. in its greatest diameters, and many smaller rounded densities were demonstrable adjacent to the nodule. The edges of these densities were not discrete or sharply

Fig. 3.—Right lung: The upper lobe contains a large aneurysm, extending to the pleura and adherent to it. The outer wall of the cavity was lacerated in removing the lung.

outlined but had fuzzy, blurred edges. These changes were interpreted as progression of growth in metastatic nodules.

All symptoms presented on the patient's admission were confirmed during his hospitalization. The temperature maintained a septic course, ranging from 99 to 103 F. The patient often complained of pain in the right side of his chest, especially during inspiration, and examination on January 8 disclosed dulness over the base of the right lung and suppressed breath sounds.

In addition to symptomatic and nutritional measures, roentgen therapy and sulfadiazine were given.

The patient was released, under protest, on Jan. 21, 1946 and died at home two days later, apparently of a massive pulmonary hemorrhage. His death occurred quickly, and no blood was expectorated as he died.

The final clinical diagnosis was lymphoblastoma with extension into the lungs and block of the inferior vena cava.

Autopsy.—The body was that of a well developed, fairly well nourished white boy, measuring 145 cm. in length and weighing 35 Kg. There was slight edema of the feet and the lower portions of the legs. The superficial veins of the abdomen and of the upper part of the chest were dilated. The superficial veins of the neck were not remarkable.

The peritoneal cavity contained about 20 cc. of clear, yellowish fluid, and the peritoneum was smooth and glistening. The left pleural cavity was completely filled with approximately 1,500 cc. of partially clotted blood; the right cavity contained about 50 cc. of clear, yellowish fluid. Both pleural cavities also presented numerous fibrous adhesions. The mediastinal lymph nodes were moderately enlarged and on section presented edematous, gray-red surfaces. The pericardial cavity contained about 20 cc. of cloudy, yellowish fluid.

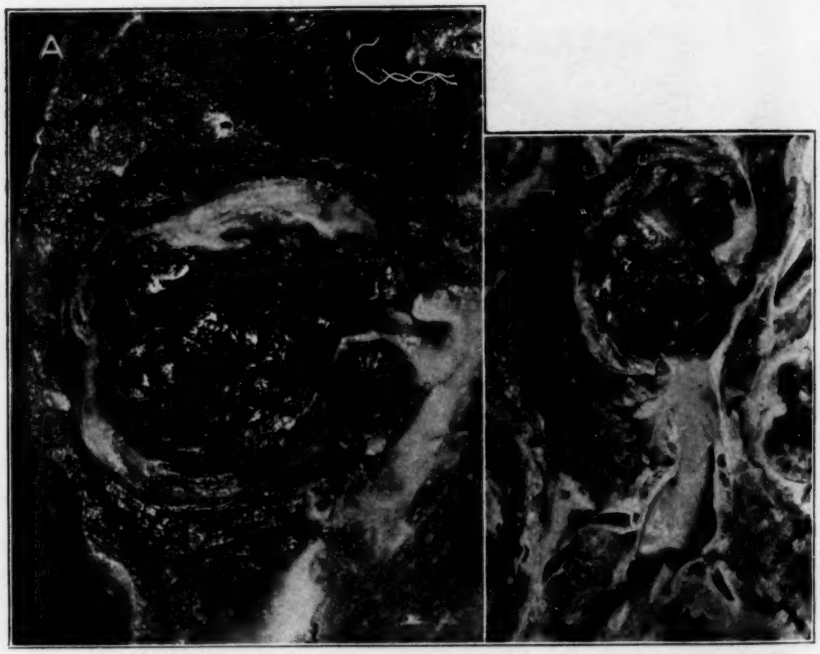

Fig. 4.—Small intrapulmonary aneurysms. (*A*) Note the thick wall and, at the right, the continuity of the aneurysm with a small branch of the pulmonary artery.
(*B*) The aneurysm arises from a medium-sized branch of the pulmonary artery.

The heart was essentially normal except for slight hypertrophy of the right side and the presence of a small mural thrombus near the apex of the right ventricle.

Both external iliac veins presented conspicuous thickening and fibrosis of their walls, and the lumen was almost completely occluded by yellowish gray, organized thrombi. These thrombi extended into the femoral veins bilaterally. The inferior vena cava presented a similar thickening of the wall. It was completely occluded by an organized thrombus in the distal few centimeters and then was distinctly narrowed (fig. 2). The superior vena cava and other veins in the region of the neck also presented thickening of the walls but appeared widely patent.

The right lung was moderately enlarged. In the lower two thirds of the upper lobe was a large, semifirm, round mass, measuring 12 cm. in diameter. On section this mass was seen to consist of a large cystic structure filled with clotted blood and organizing thrombotic material. The wall of this cavity was irregular and yellowish gray, and the lumen communicated with a small branch of the pulmonary artery (fig. 3). Throughout the lower lobe there were several nodular masses, measuring up to 5 cm. in diameter, which on section had an

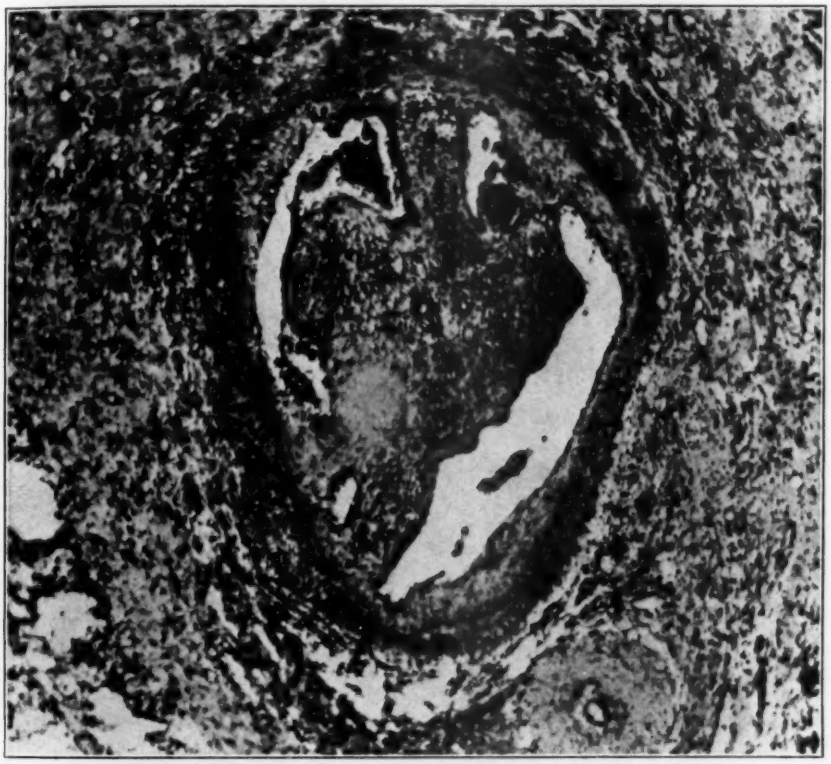

Fig. 5.—Low magnification of a small aneurysm. The lumen is almost completely obliterated by fibrous connective tissue, containing numerous lymphocytes. Note at the right a small artery with a considerably thickened wall and a narrow lumen.

appearance similar to that of the mass previously described. All these structures were attached to and communicated with branches of the pulmonary artery (fig. 4). The remaining lung tissue presented many areas of atelectasis. In the left lung the lower lobe contained a large, soft, cystic mass, measuring 15 cm. in diameter, which had previously ruptured into the pleural cavity. The lumen of this cavity was partially filled with clotted blood and organizing thrombi and communicated with a branch of the pulmonary artery. The wall of this sac measured 0.4 cm. in thickness, and its lining was irregular and yellowish. The remaining lung tissue contained an area of atelectasis and a small hemorrhagic infarct. The larger branches of the pulmonary arteries appeared essentially normal. The smaller branches, especially about the origin of the aneurysms, were greatly narrowed.

The pulmonary veins were normal. The tracheobronchial tree contained a small amount of hemorrhagic mucus. Examination of the larynx showed nothing unusual.

The spleen presented a moderate degree of lymphoid hyperplasia. The liver, including the portal and hepatic veins; the pancreas, and the gastrointestinal tract showed no gross changes.

The genitourinary system was essentially normal.

The adrenal glands and the thyroid were normal.

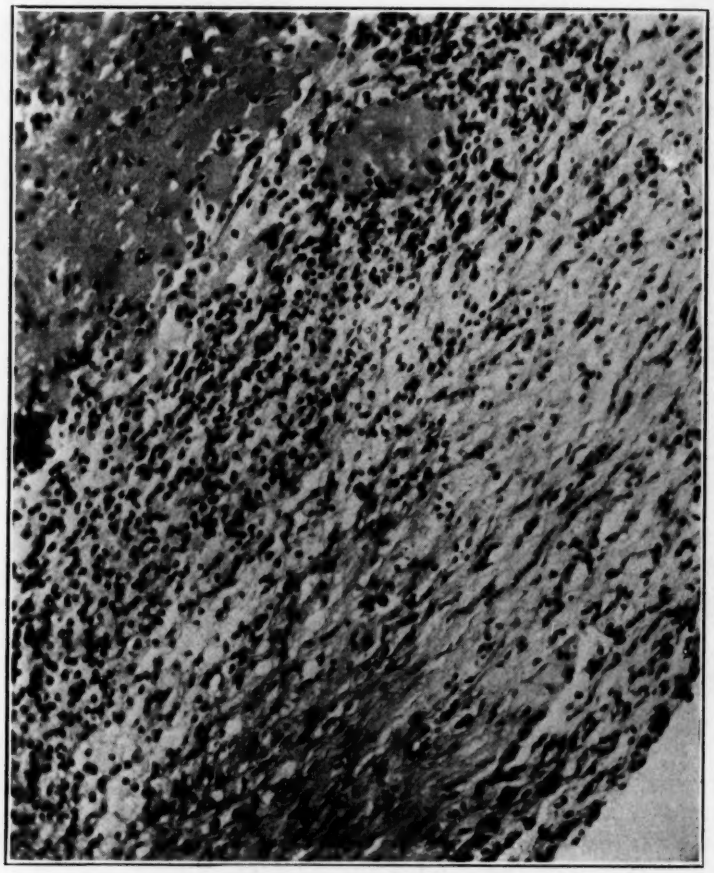

Fig. 6.—Section through the wall of a large aneurysm. Note the extensive lymphocytic infiltration and the disruption of the muscular layer.

The skull presented a defect in the right subtemporal region, and there were burr holes in both occipital regions. The dura mater in the region of the decompression was bulging. The leptomeninges appeared slightly thickened throughout. The brain was apparently normal except for softening and herniation over the right temporal lobe and for a small, superficial cortical softening in the left postcentral region.

Microscopic Examination.—Heart: There was slight hypertrophy of the muscle fibers.

Lungs: There were many areas of atelectasis, edema, hyperemia and bronchopneumonia. The small arteries presented a tremendous thickening of the wall,

with fibrosis and hyalinization. Often their lumen was partially or completely occluded by organizing and organized thrombi. Some of these thrombi were well recanalized. Around the arteries so affected there were accumulations of mononuclear cells and lymphocytes. These occasionally infiltrated the entire thickness of the vessel wall. Many medium-sized and large branches presented aneurysmal dilatations, partially filled with organized thrombi (figs. 5 and 6). These large branches also presented some degree of acute and chronic inflammation. The Masson trichrome method and Weigert stain for elastic tissue revealed pronounced fibrosis throughout the wall of the arteries, particularly in the wall of the aneurysms. In these areas, the elastic and muscle fibers were often broken down in small fragments, and sometimes were completely absent. The veins appeared essentially normal. The bronchi were often dilated, with hyperplasia of the mucosa, glands and muscle fibers.

Liver and Pancreas: No changes were observed.

Spleen and Lymph Nodes: There was hyperplasia of the lymphatic and reticuloendothelial elements.

Kidneys, Prostate, Testes, Adrenal Glands, Thyroid and Bone Marrow: These structures were normal.

Inferior Vena Cava and External Iliac Veins: There was considerable thickening of the wall, with hypertrophy of the muscle fibers of the media and interstitial fibrosis. The lumen was completely occluded by well organized and recanalized thrombi.

Brain: Examination of sections from the area of the cortical softening revealed shrinkage of the surface, loss of all normal cortical structures and replacement with glia. The blood vessels in this area presented a moderate amount of cuffing with mononuclear cells. The periphery of the lesion contained numerous pigmented macrophages. Both gross and microscopic study of the brain failed to reveal any cause for the patient's periodic intracranial hypertension.

Anatomic Diagnosis.—The diagnosis was thromboendarteritis of the pulmonary arteries, with multiple large and small mycotic aneurysms; ruptured mycotic aneurysm of the left pulmonary artery; left hemothorax; old thrombophlebitis of the iliac veins and of the inferior vena cava, with occlusion of their lumen and recanalization; small hemorrhagic infarct of the left lung; acute bronchopneumonia; hypertrophy of the right ventricle of the heart with mural thrombi; chronic lymphadenitis, cervical and mediastinal; chronic infectious splenomegaly; edema of the lower extremities; old surgical scar of the scalp, surgical bony defect of the right temporal bone and bilateral occipital burr holes; old cortical softening, and multiple fibrous adhesions in the pleural cavity.

Comment.—From the clinical picture and the autopsy observations, it is probable that this patient had two different, and apparently unrelated, diseases. The first illness, of many years' duration, was concerned principally with increased intracranial pressure. Its symptoms, following a decompression, improved but never disappeared completely. The second disease, which was the cause of death, constitutes our purpose in reporting this case.

The first symptoms of this illness appeared approximately eleven months prior to the patient's death and were characterized by a persistent, productive cough, mild chills and general malaise. Hemoptysis and dilatation of the veins of the anterior body wall appeared only several

months later. Before his admission to the hospital, the patient had also complained of pain and swelling of the left lower extremity. Eventually the child had repeated hemoptysis, but he never complained of pain in the chest or of severe dyspnea. In a more advanced stage, in spite of the septic course of the fever with severe chills, repeated blood cultures were sterile. The course of the disease may be explained in retrospect as follows: A low grade thrombophlebitis of unknown cause developed in the veins of the lower extremities and slowly extended to the inferior vena cava, which became thrombosed almost to the level of the diaphragm. Partial recanalization of the thrombosed veins took place, together with the development of an extensive collateral circulation along the superficial veins of the anterior body wall. The thrombophlebitis process apparently extended to some of these superficial veins; but, in spite of this, the anastomotic system, together with the recanalization of the veins, was almost sufficient to carry the venous return, as proved by the fact that the edema of the lower extremities was never very severe. From time to time septic emboli detached themselves from the thrombosed veins. Although not sufficiently large to cause definite clinical symptoms of pulmonary embolism, these emboli were capable of causing a true thromboendarteritis of the pulmonary arteries within the lungs. This process of severe arteritis, with destruction of the elastic and muscle fibers and their replacement by fibrous connective tissue, brought about a weakening of the arterial wall in many places and the eventual formation of multiple mycotic aneurysms. These increased progressively in size, and the rupture of one aneurysm into the pleural space was the immediate cause of death.

The pulmonary disease present in this patient and the previous occurrence of increased intracranial pressure were apparently unrelated; still, the possibility that the thrombophlebitic process affecting the large veins of the neck could have been the basis of such disorder must be taken into consideration. Unfortunately, the veins of the neck were not carefully examined at autopsy. The venous sinuses of the dura mater, and both the arteries and the veins of the meninges and of the brain, however, showed no gross or microscopic changes. The two diseases, therefore, are probably unrelated, and the increased intracranial pressure that this boy had over a period of years in his childhood, in the absence of characteristic changes in the brain or meninges, cannot be explained satisfactorily.

GENERAL COMMENT

The available reports in the literature of multiple mycotic aneurysms of branches of the pulmonary arteries with or without thromboendarteritis clearly point out the similarity of clinical pathologic observations in all such cases. The majority of such lesions occurred in young

adults and on the basis of acute or subacute bacterial endocarditis, oftener in the presence of a patent ductus arteriosus. Clinically, chills, fever, leukocytosis and tendency to bleed, with repeated hemoptysis and anemia, are present, in addition to the other signs and symptoms commonly found in bacterial endocarditis. From the pathologic point of view, the aneurysms, as a rule, are more numerous in the right lung than in the left, and they are partially or completely filled by thrombi or vegetations similar to those observed over the valves of the heart. In several instances death was the result of rupture of one of the aneurysms, either into a bronchus or into the pleural cavity.

We were able to find in the literature the report of only 1 other case in which mycotic aneurysms of the pulmonary arteries were the result of thrombosis of the veins of the legs.[6] In that case, one of a man 21 years of age, the disease lasted approximately six months, with chills, fever and hemoptysis. Autopsy revealed four aneurysms in the right lung and two smaller ones in the left lung. Blood cultures were not taken, but no bacteria were observed microscopically in the wall of the aneurysms.

Another similar case was described by Thompson and Gerstl.[7] In this case, together with thromboangiitis of the pulmonary arteries bilaterally, a large aneurysm was observed in the middle lobe of the right lung. There were no lesions of the pulmonary veins, and the peripheral veins were not examined. The patient died after severe hemoptysis. The authors considered periateritis nodosa among other etiologic possibilities. No other lesions of the periarteritic type, however, were seen in organs other than the lungs. In this case, the aneurysm developed over a period of few months, most probably as the result of the inflammatory process involving the arteries. The illness, however, was of two and one-half years' duration and had been preceded by typhoid.

A case recently reported by Castleman and Bland[8] deserves brief mention. A 44 year old woman had presented clinical evidence of cor pulmonale and slowly progressive heart failure for nine years. Postmortem examination showed localized occlusion of almost every tertiary branch of the pulmonary artery by organized and recanalized thrombi.

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6. Beattie, J. M., and Hall, A. J.: Multiple Aneurysms of the Pulmonary Arteries Following Thrombosis of the Veins of the Leg, Proc. Roy. Soc. Med. (Path. Sect.) **5**:147, 1911-1912.

7. Thompson, L. E., and Gerstl, B.: Thromboangiitis of Pulmonary Vessels Associated with Aneurysm of Pulmonary Artery: Report of Case, Arch. Int. Med. **77**:614 (June) 1946.

8. Castleman, B., and Bland, E. F.: Organized Emboli of the Tertiary Pulmonary Arteries: Unusual Case of Cor Pulmonale, Arch. Path. **42**:581 (Dec.) 1946.

Microscopically, there was no evidence of inflammatory changes in the wall of the arteries. No mention was made of dilatation. Some of the pictures accompanying this paper, however, showed lesions which, in our opinion, can be interpreted as saccular or fusiform aneurysms of the pulmonary arteries and which were strikingly similar to some of those observed in our case. Castleman and Bland suggested that these lesions were probably the result of fine emboli arising either from the pelvic veins or from the veins of the lower part of the legs.

Except in these cases, the aneurysms of the pulmonary arteries in all other reported cases were definitely congenital or, an etiologic factor, such as bacterial endocarditis, tuberculosis or, much more rarely, syphilis, was clearly recognized.

In our case, the aneurysms were probably not congenital, since fluoroscopic examination of the chest a few years before the clinical onset of the disease showed no abnormality. A congenital anomaly of the arterial wall, such as an abnormal weakness or a defect of the muscularis, however, cannot be entirely ruled out. It is also impossible to exclude the possibility that very small aneurysms were congenitally present in the pulmonary arterial tree.

Histologically, some of the small arteries in the lungs presented changes compatible with those observed in chronic healing periarteritis nodosa. However, the circumstances of such finding and the entire absence of such a lesion in organs other than the lung allows us definitely to rule out such a possibility.[9]

Thromboangiitis obliterans can also be excluded. There was some thickening of the wall of many small pulmonary veins, but this was interpreted as secondary to disturbances of the circulation within the lungs. The arterial lesions were certainly not characteristic, and, although the small blood vessels of the extremities were not examined, there was no clinical evidence of thromboangiitis obliterans to warrant such a diagnosis.

No spirochetes or bacteria were noted within the wall of the affected arteries or within the occluding thrombi. Nevertheless, we must assume that the arteritic lesions probably originally occurred on the basis of infected emboli, since, to our knowledge, aneurysm of the pulmonary arteries on the basis of noninfected emboli has never been reported. The absence of bacteria in the lesions many months after the onset of the disease certainly does not rule out such a possibility.

Of interest is the fact that, in spite of the numerous arterial occlusions and the profoundly disturbed circulation in the pulmonary arteries, only one small, recent infarct was observed within the lungs. The absence of more numerous pulmonary infarcts can best be explained

9. Eskelund, V.: Periarteriitis nodosa der Pulmonalarterie und primäre Pulmonalsklerose, Acta path. et microbiol. Scandinav. **19**:13, 1943.

by the probable slowly progressive nature of the occlusions and, in addition, the absence at any time of chronic passive hyperemia within the lungs.

The repeated attacks of hemoptysis that the patient had during the last period of his illness are probably explained on the basis of rupture of small blood vessels and capillaries, with resulting hemorrhage within the alveoli or within the bronchi. Of course, the erosion of small aneurysms within the lumens of small bronchi should also be considered, although autopsy revealed no such evidence.

The lack of pathognomonic or reasonably characteristic roentgenographic findings in cases of the entity under discussion, together with the rarity of the disease, deprived the roentgenologist of an opportunity to suggest the correct diagnosis. According to Barnes and Stedem,[10] in their study of aneurysms of branches of the pulmonary arteries, a characteristic differentiating point of peripheral pulmonary aneurysms is the demonstration of a definite vascular connection of the areas of density with the hilus. Such a diagnostic point was not demonstrated in the present case. It would be difficult to make any interpretation other than that of a metastatic malignant growth on the findings in the case presented, especially in view of the history. In retrospect, the fact that the borders of the homogeneous densities did not possess sharp edges, but had blurred outlines, should have suggested a possible inflammatory process as the underlying cause. Intravenous injection of radiopaque material, followed by its visualization in the masses within the lungs, might possibly have confirmed or disproved a diagnosis of pulmonary aneurysms.

SUMMARY

A case of thromboendarteritis of the pulmonary arteries with multiple mycotic aneurysms within the lungs is reported. The clinical, pathologic and roentgenologic aspects of this condition are briefly discussed.

Such a condition is extremely rare, occurring more frequently on the basis of bacterial endocarditis and only exceptionally on the basis of thrombophlebitis, as in this case.

The clinical and roentgenologic findings are not characteristic, and cases in which the diagnosis was made in life have not been reported. Such a diagnosis, however, should be thought of in cases of bacterial endocarditis and chronic thrombophlebitis when pulmonary symptoms, such as hemoptysis, associated with atypical pulmonary shadows in the roentgenograms of the chest are observed.

Army Medical Nutrition Laboratory, 1849 West Pershing Road (9) (Dr. Pirani).

10. Barnes, J. M., and Stedem, D. E.: Multiple Aneurysms of the Smaller Branches of the Pulmonary Artery, Am. J. Roentgenol. **30**:443, 1933.

PAROXYSMAL TACHYCARDIA IN AN INFANT WITH WOLFF-PARKINSON-WHITE SYNDROME

JAMES F. SCHIEVE, M.D.*
DURHAM, N. C.

SINCE 1925 [1] paroxysmal tachycardia in infants has been reported infrequently and sporadically. In 1941 Hubbard [2] published the classic study of paroxysmal tachycardia in infants and emphasized the distinct clinical syndrome produced by this disorder. He further emphasized that failure to determine the heart rate accurately may result in a faulty diagnosis of pneumonia or of congenital idiopathic hypertrophy of the heart, and that the underlying disorder of heart rhythm and rate may go unrecognized and untreated.

The infant in this case was at first believed to have pneumonia. The importance of the rapid heart rate went unrecognized, as the clinical syndrome was not suspected in so young a child. For this reason, it was deemed wise to report this case and to reemphasize a distinct clinical disorder observed in young infants, which usually responds promptly to proper therapy.

Until 1946, no cases of the Wolff-Parkinson-White syndrome had been reported in infants. Since then, 2 cases,[3] both of infants 14 weeks old, have been reported. One of these infants [3b] died during an attack of tachycardia. Autopsy revealed that this infant had two aberrant muscle bundle conduction pathways, or bundles of Kent, one connecting each auricle with its corresponding ventricle.

The infant in the present case was first discovered to have anomalous atrioventricular rhythm (Wolff-Parkinson-White syndrome) at 5 weeks of age, after recovery from an attack of paroxysmal tachycardia. The characteristic short P-R interval and prolonged QRS complex per-

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* Formerly Captain, Medical Corps, Army of the United States, now at Duke Hospital, Durham, N. C.

1. Werley, G.: Paroxysmal Tachycardia, with a Ventricular Rate of 307, in a Child 4 Days Old, Arch. Pediat. **42**:825, 1925.

2. Hubbard, J. P.: Paroxysmal Tachycardia and Its Treatment in Young Infants, Am. J. Dis. Child. **61**:687 (April) 1941.

3. (*a*) Bodlander, J. W.: The Wolff-Parkinson-White Syndrome in Association with Congenital Heart Disease: Coarctation of the Aorta, Am. Heart J. **31**:785, 1946. (*b*) Kimball, J. L., and Burch, G.: The Prognosis of the Wolff-Parkinson-White Syndrome, Ann. Int. Med. **27**:239, 1947.

sisted in repeated electrocardiographic tracings taken over a period of three months following the paroxysm of tachycardia.

REPORT OF CASE

S. T., a 5 week old girl, had been born normally, of healthy parents. The weight at birth was 7 pounds 2 ounces (3,132 Gm.). There were no postnatal disturbances.

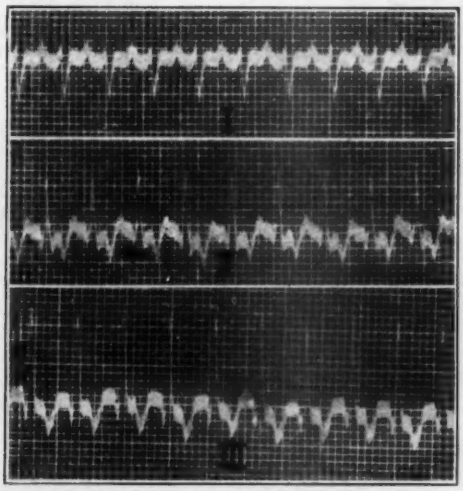

Fig. 1.—Electrocardiogram of 5 week old infant showing a paroxysmal supraventricular tachycardia with a rate of 245 per minute, taken on admission to the hospital.

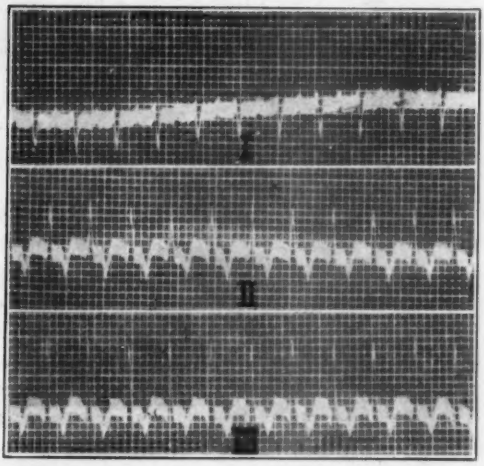

Fig. 2.—Electrocardiogram at the height of congestive failure, taken eighteen hours prior to the end of the paroxysmal tachycardia and showing a rate of 274 per minute.

The infant was breast fed and gained normally. Her weight was 8 pounds 12 ounces (3,969 Gm.) at the time of admission to the hospital on Oct. 8, 1947.

Two days before admission she vomited her feedings, refused to nurse, appeared listless and slept most of the day. The next day the same complaints persisted. The family physician saw her and noted rapid breathing and a heart rate of approximately 200 beats per minute. However, after a successful nursing in the physician's office, the infant breathed more normally, and the pulse rate slowed. During the night before and the early morning of the day of admission to the hospital the baby refused all nourishment, presented slight abdominal distention and had six episodes of rapid, labored breathing. The parents believed that the

Fig. 3.—Electrocardiogram four hours after the cessation of supraventricular tachycardia, showing a rate of 127 per minute and the Wolff-Parkinson-White syndrome.

infant had "colic." She again vomited. At 6:30 a. m. she became cyanotic. The cyanosis persisted until her admission to the station hospital at 11 a. m.

The temperature on admission was 98.6 and the respiratory rate 120 per minute, and the heart rate at the precordium was believed to be between 160 and 200 per minute. The carotid pulse was palpable, but the radial pulse was not. The baby was extremely limp and listless. The most obvious physical finding was a diffuse, mottled, ashen cyanosis of the entire cutaneous surface. She appeared to be critically ill and was panting rapidly. The heart rate was extremely rapid, and no murmurs were discernible. The pulmonary fields were clear. The edge of the liver was palpated 3 fingerbreadths below the right costal margin. Moderate abdominal distention was present, but there was no muscular spasm. There were no other abnormal physical signs.

The initial working diagnosis was that of pneumonia or septicemia. The infant was immediately placed in an oxygen tent, but there was only slight improvement in color during the first hour. An intramuscular injection of penicillin, 20,000 units, was given immediately and was repeated at three hour intervals for the next five days.

On admission, the white blood cell count was 32,100, with 12 polymorphonuclear leukocytes, 4 stab forms and 88 per cent lymphocytes. A roentgenogram of the chest, taken with a portable x-ray unit, did not reveal any pneumonic process.

The absence of high fever and roentgenographic or physical evidence of pneumonia aroused suspicion as to the basic nature of the disorder. After repeated

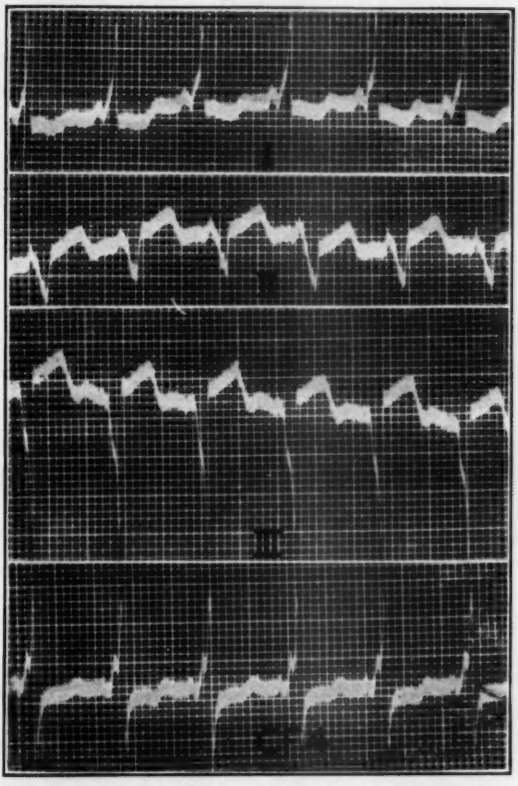

Fig. 4.—Electrocardiogram showing the Wolff-Parkinson-White syndrome with a rate of 124 per minute, taken five days after tachycardia stopped.

attempts to count the heart rate it was recorded as over 200 per minute. An electrocardiogram taken six hours after the child's admission to the hospital revealed a supraventricular tachycardia of 245 per minute (fig. 1). All attempts to slow the rate by mechanical stimulation of the vagus were without avail.

The following morning the heart rate as determined by electrocardiogram was 274 per minute (fig. 2.) A roentgenogram of the chest showed conspicuous cardiac enlargement (fig. 6 *A*). The baby was given 0.5 cc. digalen® (the cardioactive principle of digitalis, as isolated by Cloetta), ¼ cat unit, or 0.19 U. S. P. digitalis unit, intramuscularly. This was repeated at four hour intervals throughout the day. At 10 p. m. no change in heart rate was noted after 1 cat unit (0.76 U. S. P. unit)

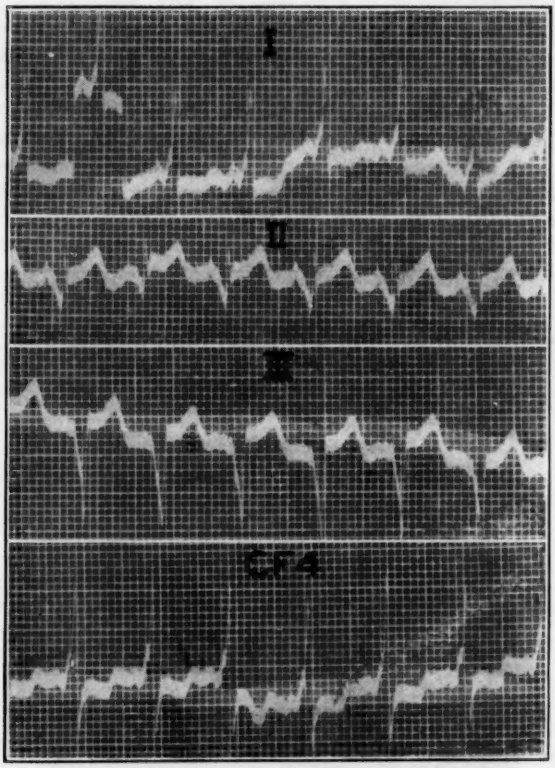

Fig. 5.—Electrocardiogram taken two weeks after end of paroxysmal tachycardia, showing the persistent Wolff-Parkinson-White syndrome.

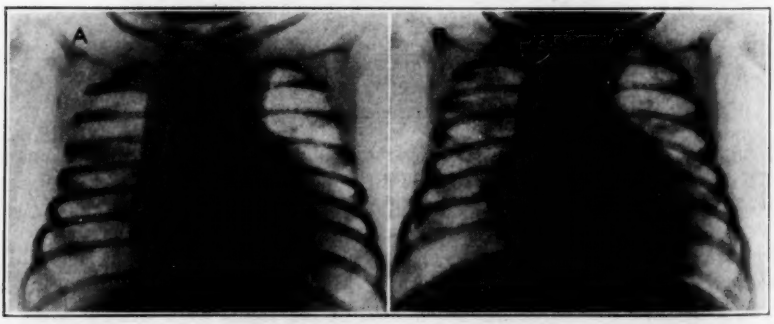

Fig. 6.—*A*, conspicuous dilatation of the heart at height of congestive failure; *B*, taken five hours after cessation of supraventricular tachycardia; decrease of approximately 1 cm. in size of the heart.

of digalen® had been given. The signs of heart failure were even more pronounced, with detectable clinical enlargement of the heart, enlargement of the liver to below the umbilicus and a spleen palpable 1 fingerbreadth below the left costal margin. At 3 a. m. of the third day of hospitalization the heart rate remained unchanged and a

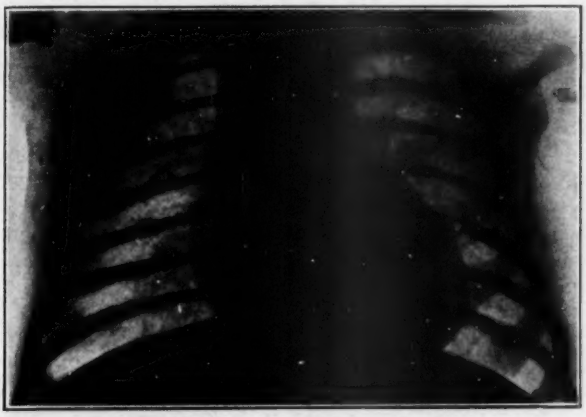

Fig. 7.—Roentgenogram showing appreciable decrease in size of the heart two weeks after recovery from supraventricular tachycardia.

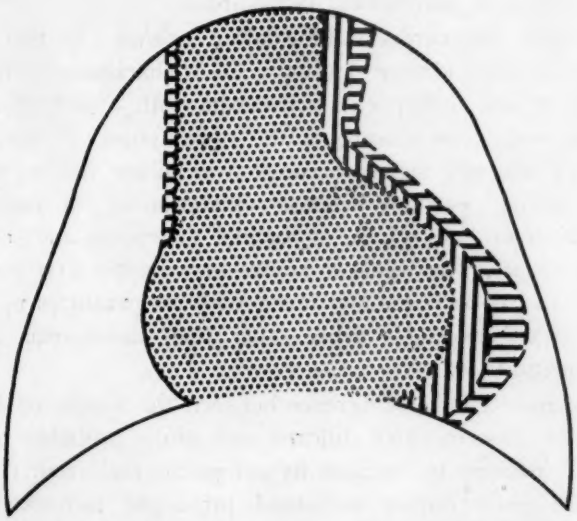

Fig. 8.—Diagram of superimposed roentgenograms, showing progressive decrease in size of the heart.

The cross hatched area indicates the size of the heart at the height of congestive failure; the vertically lined area, the size of the heart five hours after paroxysmal supraventricular tachycardia had ended, and the dotted area, the size two weeks after the attack of paroxysmal tachycardia had ended.

fifth injection of digalen® was given. At 6 a. m. the patient was observed by the mother to be much improved, and her normal pink color had returned. During examination by the medical officer, she remained pink while out of the oxygen tent.

The pulse rate was 140 (fig. 3) and the respiratory rate 40, and she eagerly drank 6 ounces (150 cc.) of water. During the day there was rapid decrease in the size of the liver, and the spleen was no longer palpable. A roentgenogram of the chest (fig. 6 *B*), taken approximately five hours after clinical improvement was noted, showed a decrease of approximately 1 cm. in the size of the heart. A final injection of digalen® (¼ cat unit) was given that morning, making a total of 1½ cat units (1.2 U. S. P. digitalis units).

The remainder of her stay at the hospital was uneventful. On the fourth day the edge of the liver was palpable at the costal margin. The heart sounds were normal, and there were no murmurs. At no time was she observed to have rapid breathing. The heart rate remained between 100 and 140 per minute (fig. 4). She was discharged on the eighth day of hospitalization. An electrocardiogram (fig. 5) taken two weeks after the attack showed persistence of the short P-R interval and prolongation of the QRS complex. A roentgenogram (fig. 7) showed a heart of essentially normal size. No further attacks of tachycardia occurred during the subsequent three months.

COMMENT

It is always difficult to count a pulse rate above 160 per minute. The difficulty is increased with a crying, squirming infant. An abnormal tachycardia in infants may be easily missed if an estimated rate is accepted or if the rate is recorded as "too fast to count" and given no further consideration. Rates over 200 per minute in infants should arouse suspicion of paroxysmal tachycardia.

Paroxysmal tachycardia is unusual in infancy. In this age group a definite clinical syndrome develops. It is characterized by vomiting and refusal to eat, tachypnea; tachycardia with a rate of 220 to 300 per minute, and often absence of the radial pulse. If the rapid rate persists long enough, signs of congestive failure follow, with rapid, labored breathing, extreme cyanosis, dilatation of the heart, enlargement of the liver and spleen, abdominal distention and, occasionally, dependent edema. The signs of failure may be the first manifestation of the illness. Leukocytosis and fever, with temperatures up to 102 F., develop without detectable cause other than tachycardia and failure of the circulation.

The apparent clinical difference between the syndrome as observed in infants and that in older children and adults probably results from the infant's inability to vocalize its symptoms and from the fact that the infantile heart cannot withstand prolonged tachycardia without early dilatation and resulting circulatory failure. That paroxysmal tachycardia of infants is usually from 40 to 100 beats per minute faster than that of adults is certainly another precipitating factor in heart failure.

An attack may end suddenly without any treatment, or it may persist, with resultant death of the patient from heart failure. According to Hubbard, digitalis is effective in terminating the attack. In view of the alarming and disastrous results that have been reported

from the use of quinine [4] and methacholine chloride (mecholyl chloride®) [2] digitalis is certainly the drug of choice. Quinidine is said to be of no value [2] in treatment of paroxysmal tachycardia of early infancy. However, its use has repeatedly been successful in 1 case [3a] of paroxysmal tachycardia with the Wolff-Parkinson-White syndrome. It has generally been noted that in infants, manual stimulation of the vagus for reflex termination of the abnormal rhythm is not effective.

SUMMARY

A case of the Wolff-Parkinson-White syndrome with supraventricular paroxysmal tachycardia in a 5 week old infant is presented. Prompt recovery of the paroxysmal tachycardia followed digitalis therapy.

The characteristic syndrome of paroxysmal tachycardia in infancy is reemphasized.

Duke Hospital.

4. Scott, E. P., and Limper, M. A.: Paroxysmal Tachycardia: Report of Two Cases in Infants, J. Pediat. **28**:96, 1946.

Progress in Pediatrics

NORMAL AND PATHOLOGIC PHYSIOLOGY OF THE BONE MARROW

WOLF W. ZUELZER, M.D.
DETROIT

IN THE last two decades a considerable amount of data concerning the bone marrow has been accumulated by anatomists, physiologists, hematologists and pathologists. The clinical application of this information was made possible by the introduction of a simple and harmless technic for the collection of samples of marrow. Arinkin's procedure, introduced in 1929, is used with minor modification by most students of the bone marrow in preference to other methods, and today the value of the diagnostic marrow puncture in certain diseases of the blood and blood-forming organs is universally accepted. It is true that many conditions affecting the circulating blood can be accurately diagnosed and evaluated by the conventional methods of study, and it should be stressed at the outset that in practice the examination of the bone marrow can only supplement but never replace the study of the blood. Like all laboratory procedures, the results of the bone marrow studies must be evaluated against the background of the complete clinical picture. However, the clinical manifestations of anemias, leukemias and other so-called blood dyscrasias are often uncharacteristic, and the blood picture does not always reflect the true state of the hemopoietic organs. For these reasons, the direct study of the marrow organ, properly applied and subject to certain well understood limitations, has become an indispensable, though by no means infallible, tool of the modern hematologist.

Apart from its diagnostic application, the study of samples of bone marrow obtained by single or repeated punctures has provided a direct method of investigating the function of the marrow organ. Physiologic and pathogenic mechanisms which formerly had to be inferred from the blood picture, or often enough remained altogether obscure, have been clarified to a large extent by the study of aspirated bone marrow. Even today, however, the knowledge of marrow function under nor-

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From the Anemia Clinic of the Children's Hospital of Michigan and the Department of Pediatrics, Wayne University College of Medicine.

mal, as well as pathologic, conditions is far from complete, and its application to clinical medicine must be undertaken with considerable caution. The bone marrow is a complex and, even under normal conditions, highly variable organ. Its cellular composition is not homogeneous and profound changes can occur with great rapidity. The present quantitative methods of investigation are, without exception, relatively crude and beset with large inherent errors. In spite of considerable progress some basic questions are as yet unsolved, such as the release mechanisms of the cells from the marrow and the origin, function and even the nomenclature of some of the marrow cells. Thus, any theory of marrow function is of necessity based, to some extent, on unproved assumptions, and the state of knowledge does not justify dogmatic assertions. Admittedly, any attempt to present a comprehensive view of this subject will be colored to some extent by personal experience, by the methods used for study and by habits of thinking. Simplifications and perhaps oversimplifications will be inevitable in the course of this discussion. Credit should be given to the great Swiss hematologist Rohr [1] from whose concepts of marrow physiology I have freely borrowed.

I. ANATOMY, HISTOLOGY AND CYTOLOGY OF THE MARROW

A. Anatomic Structure.—In the human embryo, as in lower animals, the formation of blood cells is not the well localized function of a single organ but is at first quite ubiquitous. The localization of hemopoiesis and the evolution of the marrow as a definite organ is a gradual process which is completely finished only at birth. At various periods blood formation takes place in the yolk sac, the primitive vascular mesenchyma, the spleen, lymph nodes, thymus and liver. During the middle part of fetal life the liver is the chief site of formation for red blood cells. The hemopoietic activity of the bone marrow begins as early as the third month but is at first confined to the production of leukocytes. Gradually, the activity of the liver declines and the bone marrow becomes the sole site of formation of both leukocytes and erythrocytes, but even after birth the mesenchyma at the sites of fetal blood cell formation can resume hemopoiesis under certain conditions, the more readily the younger the infant, that is, the closer to fetal life. However, extramedullary hemopoiesis in postnatal life is always a pathologic phenomenon. It has a direct bearing on the interpretation of marrow studies, since it provides a possible origin other than the bone marrow for cells seen in the blood and must be taken into account especially when seeming discrepancies between the blood picture and the marrow findings are observed.

1. Rohr, K.: Das menschliche Knochenmark, Leipzig, Georg Thieme, 1940.

At birth the marrow is a sizable organ with a volume of 70 to 90 cc. At this time and throughout most of infancy it contains no fat and is composed entirely of hemopoietic tissue. The conversion of red to yellow marrow is a gradual process which can be demonstrated at first only microscopically. At the age of 3 to 4 years the admixture of fatty marrow begins to be grossly noticeable in some of the long bones, but at 5 to 7 years a substantial portion of the marrow of the tibia is still cellular. At maturity the marrow of the tubular bones is yellow and red marrow is confined almost entirely to the vertebrae and the flat bones, such as the skull, sternum, ribs and scapulas. Even this portion of the marrow normally consists of approximately 50 per cent fat cells, so that in the adult only one quarter of the total marrow volume of 3,000 cc. is composed of hemopoietic tissue. However, with increased hemopoietic activity the proportions can change rapidly, as active red marrow expands at the expense of the fat.

B. Histologic Picture.—The histologic structure of the marrow is that of a delicate mesh of reticulum fibers anchored here and there to reticulum cells. The hemopoietic cells which form the parenchyma proper seem to lie free in the spaces of this mesh. The vascular channels of the marrow, in contrast to those of the spleen, form a completely closed system. The fact that there is no communication between the reticular spaces and the lumens of the vessels implies the existence of special mechanisms for the release of cells from the marrow parenchyma into the circulation. In the opinion of some workers this process takes place in the sinusoids, wide, thin-walled vessels connecting the arterial capillaries with the veins of the marrow. The lining of these sinusoids consists of a special type of endothelial cells derived from reticulum which are connected with the stromal reticulum by delicate fibers and which behave generally like reticulum cells, especially in their ability to store dyes. The potential volume of the combined lumens of the sinusoids is so large that in the rigidly enclosed marrow spaces only a part of them can be dilated at the same time. Thus, a considerable number of these vessels are always collapsed.

The nerve supply of the marrow organ seems to have received comparatively little attention. There is some evidence that both sympathetic and parasympathetic fibers enter the marrow, but their anatomic demonstration is difficult. The fat cells of the marrow are considered as reticulum cells which have stored fat. The ability of these cells to take up or give up fat rapidly accounts to a large extent for the great variations in the cellularity of the marrow.

C. Cytologic Appearance.—The bone marrow contains a large variety of cell types, some native, others probably carried there by

the blood stream. The classification of these elements has been unnecessarily complicated by the use of different systems of nomenclature by the various writers. The end products of cellular division in the normal marrow are chiefly erythrocytes, granulocytes and platelets, and most of the marrow cells are readily identified as precursors in one of these three series. Thus the numerous cell types are easily reduced to a few basic categories, each subdivided on the basis of progressive cellular maturation. Difficulties arise mainly in the classification of the few remaining cells too primitive to indicate the direction of their development by morphologic characteristics. The protracted controversy about the origin of the blood cells centers on the nature of these stem cells. The so-called unitarians assume the existence of a common ancestral cell for all the various blood cells, including lymphocytes and monocytes. Adherents of the polyphyletic school deny the existence of a totipotential cell and postulate several functionally, if not morphologically, distinct stem cells, each strictly limited in its specificity and capable of development in only one direction. These arguments have magnified the problem beyond its clinical significance. Neither side has been able to prove its contention on morphologic grounds. The gap between the divergent opinions is being narrowed. Through the fog of terminology a middle ground is becoming visible on which the unitarian will concede the specificity of separate ancestor cells for the development of blood cells under ordinary conditions and the polyphyletic school will admit that under certain pathologic conditions regeneration can begin at the level of a completely indifferent, totipotential stem cell.

Lymphocytes are always evident in the bone marrow and probably originate in part from the marrow reticulum, although the majority are derived from the reticulum of the lymphatic organs proper. The presence of discrete nodules of lymphatic tissue in the marrow is accepted by nearly all authorities, but in routine sections such nodules are so rarely seen that workers cannot account for the regular presence of lymphocytes, or at least of cells indistinguishable from lymphocytes, in aspirated material. These cells are probably scattered diffusely through the parenchyma or the marrow.

Monocytes, never numerous in the normal marrow, are regarded by some authorities as relatively primitive cells formed ubiquitously in the reticuloendothelial system and not represented by precursors among the free myeloid cells of the marrow. Other authors, notably adherents of the Nägeli school, consider the monocyte as a genuine marrow element derived from myeloblasts or possibly from a specific stem cell, the so-called monoblast. The argument, while of considerable theoretic importance, has little bearing on clinical problems.

II. CELLULAR COMPOSITION OF NORMAL MARROW

There is no reliable measurement of the cellularity of aspirated marrow samples. The variable admixture of fat and blood makes large variations in total counts almost inevitable. The figures given vary enormously.[2] Only very pronounced deviations from the average can, therefore, be significant. Increases are more likely to be meaningful than decreases, which may be due to dilution of the marrow with blood. The few available figures suggest that the marrow of infants and young children gives higher counts than that of persons from other age groups. From what has been said about the histologic evidence, this is to be expected.

The differential distribution of the marrow cells is more likely to be informative, but it also varies within wide limits. The various authors used different criteria for the identification of cells. Admixture of cells from the blood can influence the picture. Here too, only major deviations from average standards can be significant. Differences in the cellular composition of the marrow between children and adults have been no more pronounced than those observed within each age group. At best it can be said that the number of lymphocytes in infantile marrow seems to be consistently higher, and several authors reported a slight increase in the number of immature cells.

In the evaluation of percentages and ratios among marrow cells, it must be remembered that a relative increase of one cell type may be due to the decrease of another. The most significant ratio is that of the total number of granulocytes to erythroblasts, which is usually given as 3 or 4:1. In the newborn with highly active erythropoiesis this ratio is normally much lower, approximately 1:1, but it changes rapidly in the first few weeks in keeping with other evidence of reduced regeneration of the blood during this period. After this time, the cellular picture of infantile marrow differs in no important respect from that of the adult.

On the whole then, qualitative alterations are more dependable than quantitative changes. Nevertheless, by strict adherence to a chosen procedure, trends can be followed in serial and group studies, and quantitative data, if cautiously interpreted, can often give valuable information even in single examinations. Clinical experience has shown that with rare exceptions samples of marrow obtained by puncture are representative of the marrow as a whole and the assumption that the marrow reacts in a uniform, organ-like manner is justified for practical purposes.

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2. Osgood, E. E., and Seaman, A. J.: The Cellular Composition of Normal Bone Marrow as Obtained by Sternal Puncture, Physiol. Rev. **24**:46, 1944.

III. PHYSIOLOGY OF THE MARROW

The three main cell systems of the marrow, erythropoiesis, leukopoiesis and thrombopoiesis, are to a large extent independent of one another and often react in an opposite way to the same stimulus. Infection, for example, may depress erythropoiesis and stimulate leukopoiesis. Isolated disturbances in thrombopoiesis are common. On the other hand, the entire marrow may react as a unit, for example, in aplastic anemia, in which the formation of all the blood elements is suppressed, or in the response to hemorrhage, when platelets and leukocytes, as well as erythrocytes, are produced in increased numbers.

The interrelations of the marrow with other organs are largely obscure. It is assumed that the spleen exerts a certain inhibiting influence on the marrow, especially in thrombopenic purpura, in which actual changes in the megakaryocytes have been reported. Other direct hormonal influences have been suspected but never proved. The nervous control of marrow function has received little attention. Increase in cellularity after sympathectomy and the opposite effect after elimination of parasympathetic ganglions suggest that the sympathetic nerves inhibit and the parasympathetic ones stimulate marrow function.

The degree of erythropoietic activity seems to be regulated largely by the oxygen tension prevailing in the marrow. Anoxia regularly increases erythrocyte regeneration, whether it is produced by loss of blood, circulatory conditions, reduced atmospheric oxygen tension, pulmonary disorders, repeated exercise or increased tissue metabolism, as in hyperthyroidism. All these conditions, unless complicated by other factors, tend to produce erythroid marrow hyperplasia. Increase in tissue oxygenation is difficult to produce, but reduction of oxygen consumption, as in hypothyroidism, is accompanied with decrease in erythropoiesis and, accordingly, with anemia.

Direct stimulation of erythropoiesis under conditions excluding anoxia has not been demonstrated. Iron or other so-called hemopoietic substances do not stimulate the marrow in normal persons and seem to act only by restoring normal response to a previously deficient marrow already stimulated by anemic anoxia, as shown by hyperplasia before therapy.

In the regulation of leukocyte regeneration, various hypothetic and actual substances have been described as effective chemotactic stimuli for the migration of mature leukocytes from the marrow. Leukocyte maturation factors for the regeneration of the young granulocytes have also been demonstrated. Because of the direct influence of many factors, nervous, humoral, toxic and infectious, that can rapidly change the leukocyte content of the blood, a correlation of

the findings in marrow and blood is often difficult. Leukocytosis always seems to indicate increased marrow production, but leukopenia may go with hyperplasia, as well as with hypoplasia, of marrow granulocytes. Normally, to speak in the broadest possible terms, production is regulated by demand. The same seems true of platelet formation by megakaryocytes, but the meaning of changes in this cell system is as yet poorly understood. It is not at all clear, for example, why pneumonia is almost invariably accompanied with an increase in megakaryocytes in the marrow. The whole chapter of the physiology of the marrow is full of unsolved questions and contains few established facts.

The function of producing cells for the circulating blood implies a degree of cellular regeneration far greater than that of most glandular organs which retain their cellular composition in the process of secretion. The regeneration of the blood elements moreover is not a process of simple reproduction of cells but involves three distinct steps: (1) the multiplication of precursor cells; (2) the evolution of the definitive characteristics of the blood cells, enabling them to carry out their specific tasks in the body, i. e., maturation, and (3) the release of the mature elements. These partial functions must be properly integrated to assure the orderly replacement of formed elements of the blood and to provide a potential reserve for the variable demands of the body. Theoretically, disturbances can result from failure of each of these partial functions, or from lack of coordination among them. Therefore, it is pertinent to examine separately each of the three steps.

1. Multiplication of Precursor Cells.—The multiplication of cells destined for the circulating blood occurs chiefly, if not exclusively, by mitotic division. In smears or sections of fresh marrow, mitotic figures are nearly always demonstrable. They are normally more numerous in erythroblasts than in young granulocytes, indicating that the erythroblasts divide more frequently and perhaps more rapidly. This explains the apparent paradox that many more erythrocytes than leukocytes are produced, although the marrow contains fewer erythroblasts than leukocyte precursors. Divisions of megakaryocytes are infrequent. This is not surprising, since a single megakaryocyte forms large numbers of platelets, whereas only one red cell or leukocyte is produced by the maturation of a nucleated cell in the marrow.

Mitotic division is not confined to any particular type of marrow cells but can occur in primitive as well as in highly developed cells. Only in the end stages of maturation is the ability to divide lost by the aging cells. Thus, metamyelocytes and orthochromatic erythroblasts are not usually capable of mitotic division. Ordinarily, mitotic

proliferation is most intense at the level of the polychromatic erythroblasts and neutrophilic myelocytes, i. e., in cells which are already differentiated to a high degree. The ability of these elements to multiply insures a reserve of cells already in an advanced stage of development, in other words, cells whose short maturation period makes them almost immediately available for delivery to the blood. The reserve produced by multiplication of the more primitive cells is not so readily available because these elements need more time to complete their maturation. Thus, the young basophilic erythroblasts and promyelocytes represent a second line of defense.

Ordinarily, the predominant mode of cell division in the marrow is homoplastic, i. e., the divisions produce daughter cells with the same characteristics as the mother cells. In times of stress the number of homoplastic divisions increases, but possibly the normal marrow can also fall back on another mode of reproduction which is usually predominant only in the embryo, namely heteroplastic division, i. e., the formation of daughter cells with new characteristics by a sudden mutative process. Heteroplastic division combines reproduction and maturation in one step. It should increase the effectiveness of the division of primitive cells by creating more highly differentiated offsprings, i. e., cells with a shorter maturation period, resulting in a short cut to the more rapid production of mature cells.

The reserve power of the marrow organ is determined not so much by its absolute size or by its cellularity but by its ability to respond to increased demand with a general increase in mitotic activity and perhaps with the resumption of heteroplastic division. These mechanisms permit the normal marrow to adapt itself rapidly to the needs of the body. The increased demand for red blood cells created by sudden hemorrhage or hemolysis results in an increase in the mitotic activity of the polychromatic erythroblasts. If the demand is large, increasing proliferation of the more primitive basophilic cells is observed. A distinct increase in erythroblast mitosis has been demonstrated as early as one-half hour after hemorrhage. With the establishment of a new equilibrium, a shift toward more mature oxyphilic cells is brought about by maturation of many of these cells and perhaps by heteroplastic division, so that in chronic anemias due to loss of blood the number of oxyphilic erythroblasts rises. A corresponding increase in metamyelocytes in the marrow is often seen in infections if they become chronic. In conditions which are apt to put a maximal strain on the marrow over long periods, for instance, chronic hemolytic anemias, all types of erythroblasts, basophilic, polychromatophilic and oxyphilic, are increased in number.

The reaction of the leukopoietic cells to rising demands created by suppurative infections is analogous. The details of such proliferative

responses are as yet obscure. It is uncertain whether the proportion of cells undergoing mitosis is increased, whether the time interval between cell divisions is shortened or whether the process of mitosis itself is accelerated. The available evidence suggests that all three mechanisms may come into play. Certainly, the number of mitotic figures observed in the marrow in states of active regeneration often seems insufficient to account for the rapid increase in the total number of cells, and the assumption that the cells divide oftener and more rapidly appears logical. It follows that the number of mitoses seen at any one time is not necessarily an index of regenerative activity.

A decrease in the absolute number of mitoses, however, is likely to be significant and usually indicates quantitatively insufficient regeneration. A depression of mitotic activity can be brought about in various ways, chiefly by toxic and infectious influences or by physical agents, such as radiation, but it also occurs without known cause. With the decrease in cell divisions on the one hand and the continued migration of the maturing elements from the marrow into the blood on the other, the marrow becomes depleted of cells. Oftener than not, this depression involves only one group of cells and the total cellularity of the marrow may remain unchanged or may even increase if cells of another group proliferate. This is frequently the case in infections, in which the same stimulus can cause depression in the erythroid series and increased proliferation of granulocytes reflected in a blood picture of anemia and leukocytosis. In infancy and early childhood infection commonly produces such combination pictures. Severe infections may also depress the regeneration of granulocytes in the marrow and affect platelet formation as well.

The disturbances characterized by simple quantitative reduction of mitotic division constitute the true hypoplastic-aplastic conditions. These result in a so-called aregenerative blood picture; I shall discuss later the way in which similar blood pictures can arise from disturbances in marrow associated with hyperplasia. Depending on the involvement of erythroid cells, granulocytes or megakaryocytes, hypoplastic states of the marrow will result in anemia, leukopenia or thrombopenia. If all three groups of marrow cells are affected, the blood picture of so-called pancytopenia, panmyelophthisic or aplastic anemia will develop and sections of the marrow will show an increase in fat cells or, especially in younger age groups, an "empty" appearance. Aspiration in this type of case does not always give reliable information because of the spotty distribution of the cells remaining in the marrow, and, when hypoplastic or aplastic anemia is suspected, repeated punctures, or the study of surgical biopsies of marrow are necessary to establish the diagnosis.

2. *Maturation.*—Maturation and reproduction may be considered as opposing tendencies in the life of the marrow cells. These forces are expressed in a diagram (fig. 1) in which the horizontal line represents tendencies favoring division, i. e., multiplication without progress toward maturity, and the vertical line expresses maturation tendencies, i. e., progressive development of cell properties without increase in numbers. This diagram is based on the assumption that the marrow cells, at least under normal conditions, will either divide or mature automatically with age but cannot stand still.

Maturation as a process distinct from cell division was defined earlier as the evolution of the definitive structural and functional characteristics of the blood cells, for instance, the hemoglobinization and denucleation of erythroblasts and the development of specific

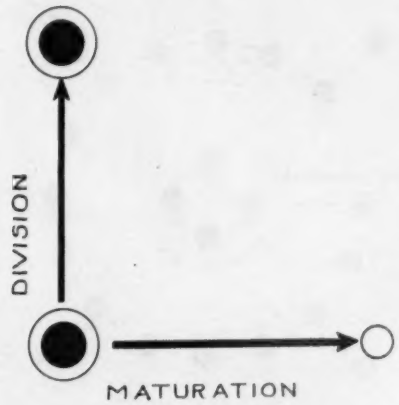

Fig. 1.—Diagrammatic representation of maturation and division as opposing tendencies in the development of hemopoietic cells.

granules, motility, phagocytosis and nuclear segmentation in granulocytes. Not all the characteristics present at maturity are necessarily developed *de novo* during the life span of the individual cell. A myelocyte, at the moment of its origin by the division of another myelocyte, is already endowed with properties which a more primitive promyelocyte must acquire by maturation. In other words, a certain degree of development can be inherited by cells at the beginning of their individual existence. Therefore, maturation must be redefined as the progressive change which takes place during the life span of the individual cell. The factors which determine whether the marrow cells continue to divide or proceed to mature are not well understood. In general, reproductive tendencies predominate in primitive cells, while the more highly developed cells tend toward final differentiation. In the intermediate stages these antagonistic tendencies seem to be fairly evenly balanced (fig. 2).

The duration of the maturation process is variable. It must depend, among other factors, chiefly on the starting point, that is, on the character of the cell which is maturing. Barring intermediate cell division, primitive cells will need more time to mature than do highly differentiated cells. For example, a promyelocyte, if it can no longer divide, ages and matures more slowly into a leukocyte than a metamyelocyte which needs little changing to become a "band" form. The long individual life of such a promyelocyte is suggested by the hypersegmentation of the nucleus which is an aging phenomenon. Similarly, a basophilic erythroblast maturing without the benefit of intermediate

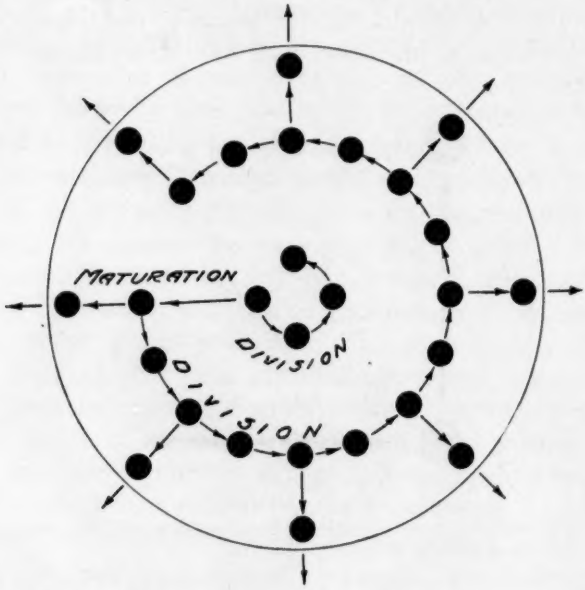

Fig. 2.—Diagram illustrating a working hypothesis of normal marrow activity. The inner row of small circles represents primitive differentiation, for instance, polychromatophilic erythroblasts, and the outer row of small circles, nearly mature cells. The large solid circle at the periphery represents the barrier between bone marrow and blood which only mature cells can pass. The circular arrows indicate division, and the radial arrows, maturation tendencies in the normal marrow. Multiplication is most active at the level indicated by the intermediate circle.

divisions will reach the stage of the erythrocyte more slowly than an oxyphilic cell, which at the time of its origin by mitosis already contains some hemoglobin. The large basophilic erythroblast becomes a much larger erythrocyte than the small oxyphilic erythroblast. The direct maturation of primitive erythroblasts, in other words, results in macrocytosis, that of polychromatic cells in normocytosis and that of small oxyphilic erythroblasts in microcytosis. The size of the red cells and the degree of nuclear segmentation of the leukocytes, as

they appear in the blood, is related to the maturation process in the marrow. The size and shape of these blood cells indicate the maturation level of their marrow precursors. Hypersegmented leukocytes suggest a promyelocytic marrow; normally segmented leukocytes correspond to a normal, myelocytic marrow, and predominance of band forms in the blood goes with predominance of metamyelocytes in the marrow. The so-called shift to the right in the blood reflects a marrow shift to the left and vice versa. Likewise, macrocytosis is the expression of a shift to the left in erythroblasts, microcytosis that of a shift to the right.

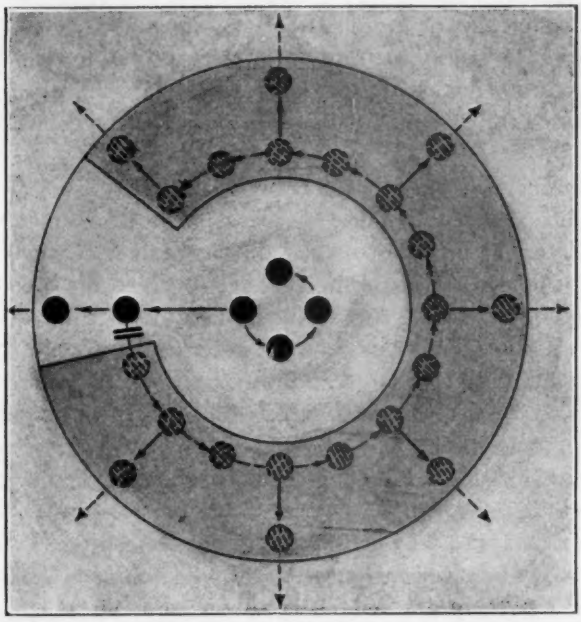

Fig. 3.—Diagrammatic representation of the marrow disturbance in pernicious anemia and megaloblastic anemias in general. Symbols are used in the same manner as in figure 2. Cell division continues at the primitive level but is interrupted at the intermediate level. The maturation time (distance from inner to outer circle) is increased.

An analysis of these relations is essential for the understanding of conditions characterized by so-called maturation arrest, particularly pernicious anemia, its counterpart in infancy, megaloblastic anemia, and agranulocytemia. Strictly speaking, the term maturation arrest is misleading. The fundamental disturbance in this group is one of regeneration and consists in the loss of mitotic function in the more highly differentiated cells, polychromatic erythroblasts and myelocytes. The less sensitive primitive cells, basophilic erythroblasts or promyelocytes, remain capable of mitosis. With the cessation of mitosis (fig. 3)

at the normally most active levels and the subsequent depletion of the more mature elements, a preponderance of immature cells develops which becomes a genuine hyperplasia as the marrow attempts to meet the increasing demands of the body. The hyperplasia of immature cells remains ineffective, partly because of the predominance of mitosis over maturation at primitive levels, so that most cells simply continue to divide but remain immature, and partly because such cells as do mature need more time to complete the process. In pernicious anemia certain observations suggest a maturation time of erythrocytes of ten to twelve days as compared to a normal average of three to four days.

The blood picture of the megaloblastic anemias reflects the marrow disturbance. The scanty maturation of large primitive cells in the marrow produces anemia with macrocytosis and, since the disturbance affects all marrow elements, leukopenia with hypersegmentation of the nuclei.

In agranulocytosis the relation between the marrow and blood picture is less readily apparent because of the rapid destruction of leukocytes in the body, but it becomes distinct during remission when the hypersegmented leukocytes precede the younger forms in the blood.

The development of marrow hyperplasia with immaturity in this group of conditions illustrates the interdependence of mitotic function and maturation. It is clear that hyperplasia of the marrow elements per se does not necessarily mean effective blood regeneration. If mitotic activity and maturation tendencies are dissociated, the production of mature cells will suffer. Not the cellularity of the marrow but the output of functional elements is the true measure of marrow function.

The marrow picture of maturation arrest is seen in the anemias due to a deficiency of antianemia principle in which erythroblastic regeneration is predominantly affected, in agranulocytosis in which myeloblasts and promyelocytes dominate the field and the regeneration of myelocytes and leukocytes is suppressed and in thrombopenic purpuras in which large numbers of immature megakaryocytes incapable of platelet formation are observed. These conditions are usually reversible.

The success of therapy with folic acid or liver in the megaloblastic anemias and possibly in certain agranulocytoses suggests that these disorders result from deficiencies or interference in enzyme systems essential for normal regeneration of marrow cells. Only a few hours after the first injection of folic acid the regeneration of erythroblasts is reestablished. Mitotic division becomes frequent, first in basophilic erythroblasts; then, as mitotic function of the more advanced cells and maturation is reestablished, numerous polychromatic cells appear, and the mitosis maximum shifts toward these more mature cells. Shortly, the oxyphilic cells become numerous, and, finally, the first wave of

mature cells appears in the blood as reticulocytes. The entire process can be followed in serial marrow studies. It reaches its climax in five to six days and is followed by a continued rise of hemoglobin and red cells in the blood, as the marrow remains hyperactive until the anemia is overcome. It is interesting that the magnitude of response in infants with megaloblastic anemia is comparable to that of adults, although it is often stated that infants lack the potential reserve of inactive yellow marrow. Actually, the adult with pernicious anemia in relapse has no advantage over the infant because his fatty reserve marrow has already been converted into active red marrow; yet this hyperplasia remains ineffective, so that when treatment is begun, the adult and the infant actually start from the same point. Once more it must be stressed that the most significant factor in determining marrow reserve is a functional, not an anatomic, one, namely, the ability of the marrow to meet increased demands with intensified rather than merely extended regeneration.

The resumption of normal leukopoiesis during the remission of agranulocytosis occurs in a similar manner.

In thrombopenic purpura of the Werlhof type the effect of splenectomy on megakaryocytes and platelets suggests an excessive or abnormal effect of the spleen on megakaryocyte maturation and, secondarily, on platelet formation. With the removal of this organ, the megakaryocytes rapidly assume a mature appearance and resume platelet production. Thus the marrow picture gives information concerning the diagnosis and often the state of function of the marrow organ in thrombopenic purpuras; no patient should be subjected to splenectomy without previous study of the bone marrow.

As stated previously, the maturation time depends at least in part on the initial character of the maturing cells. The possibility of slowing of the maturation process itself must now be considered (fig. 4). Such a disturbance, which would be a true arrest of maturation, seems to account for the changes occurring in the marrow in iron deficiency states. Hemoglobin itself appears to be a necessary factor in the maturation of erythrocytes. In the absence of available iron, the erythroblasts remain poor in hemoglobin, the denucleation seems retarded and many cells do not reach the degree of maturity necessary for their release into the blood stream. They remain in the marrow, which thus appears hyperplastic and becomes increasingly immature as less and less hemoglobin is available in the newly formed cells. In iron deficiency states the erythrocytes are at first only hypochromic, that is, the hemoglobin content of the cells decreases; but, as the maturation disturbance in the marrow progresses, fewer cells are released and the red blood cell count also drops. Again, the paradoxic combination of marrow hyperplasia with anemia is seen. Pure pictures of this type in infancy are

relatively rare however, because of the frequency of simultaneous infections which tend to inhibit the mitotic activity of erythroblasts and thus counteract the tendency to hyperplasia. Studies of marrow are seldom needed for the diagnosis of hypochromic anemias, but they may give valuable information about the response to iron that can be expected in a given case, depending on the presence or absence of hyperplasia. The hyperplastic marrow should respond promptly to iron therapy: hemoglobin is formed rapidly, the maturation of the cells is restored and shortly a reticulocytosis of the blood indicates the beginning remission.

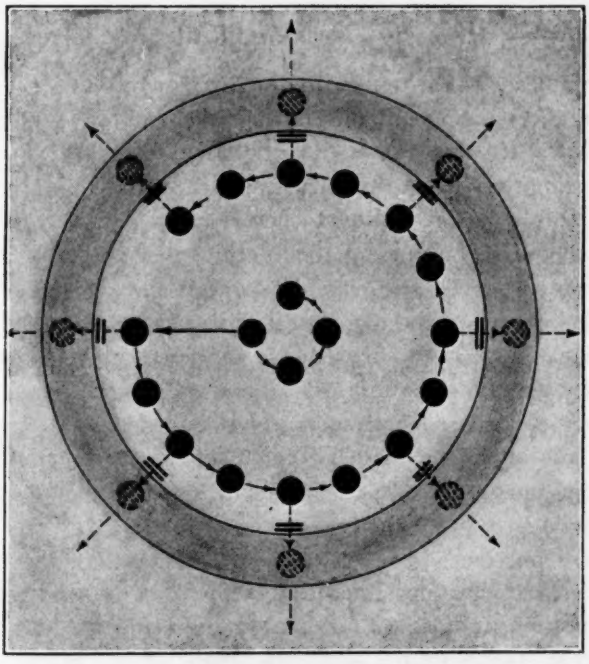

Fig. 4.—Diagrammatic representation of marrow dysfunction in iron deficiency anemia. Symbols are used in the same manner as in figures 2 and 3. Cell division continues at the level indicated by the inner and intermediate circles, but maturation is impaired; consequently fewer cells reach the periphery, while the marrow becomes hyperplastic.

One can only speculate on the meaning of the marrow hyperplasia associated with Mediterranean anemia. In the past, it has been assumed that this is a purely compensatory phenomenon associated with increased hemolysis. It seems more likely, however, that the characteristic hypochromasia of the red cells in this disease reflects an inability of the marrow cells to synthesize hemoglobin properly or in adequate amounts. The lack of this "maturation factor" should have a similar effect on the marrow as in hypochromic anemias due to exogenous iron deficiency,

and, indeed, the marrow picture of Mediterranean anemia differs only quantitatively from that seen in ordinary iron deficiency anemias.

3. The Release of Mature Elements.—The release mechanisms of cells from the bone marrow are still under debate. The migration of leukocytes can be explained by their motility, but the manner in which the nonmotile erythrocytes enter the closed circulation of the sinusoids remains in doubt. Doan, Sabin and others assumed that erythropoiesis actually takes place in the lumens of sinusoids temporarily closed off

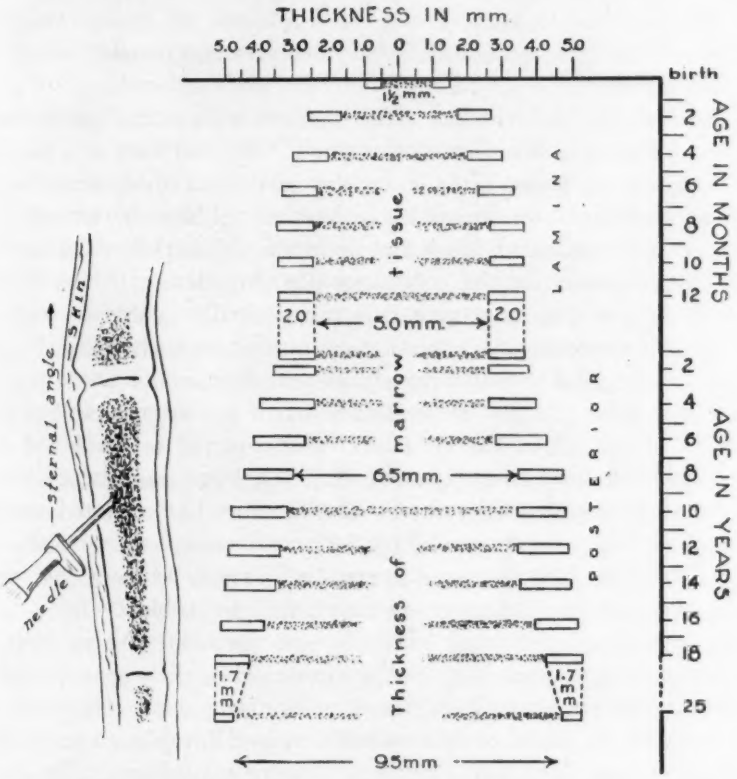

Fig. 5.—Diagram showing thickness of the lamina and sternal cavity at various ages.

from the general circulation and that the mature cells are released when the vessels expand without having to cross the capillary membranes. This theory is plausible and has the advantage of simplicity and the support of analogous observations in other hemopoietic organs, but it has not been generally accepted and does not explain all the facts. Other equally qualified investigators, especially histologists, deny intravascular hemopoiesis in the marrow and explain the release of erythrocytes from the parenchymal mesh by pressure exerted against the delicate

capillary walls by the growing clusters of erythroblasts. When the pressure is large enough, the membrane is temporarily disrupted and the mature cells are released from the gel-like matrix in which they are supposedly embedded and ejected into the lumen. This theory has the support of histologic observations, but no one has succeeded in demonstrating the process, and it must be concluded that the question has not been settled. This is equally true for the release of platelets.

Despite this serious gap in knowledge, it may be assumed that under normal conditions only mature cells can leave the marrow. The retention of immature leukocytes may be explained by poorly developed motility. The factors conditioning erythrocytes and platelets for release are not known.

Theoretically, disturbances of the marrow release mechanism might account for certain disorders of the blood. The old idea of a so-called block implies retention of cells on the basis of a dysfunction in the release mechanism or an anatomic barrier. There is, however, no anatomic basis for such a block and maturation disturbances of one type or another account for the conditions formerly designated as block.

If it is true that immature cells are normally unable to leave the marrow, the question arises in what circumstances such cells do appear in the blood. The probable answer is that even under abnormal conditions immature marrow elements remain in the marrow and that the majority, if not all, of the immature cells observed in the blood come from extramedullary sites of hemopoiesis. A large number of observations tend to support this view. The marrow has a closed vascular system, whereas in extramedullary foci communications with vascular channels exist. The release of immature blood cells from the spleen, lymph nodes or liver offers no special histologic problem.

In fetal blood nucleated red cells are abundant during the predominancy of extramedullary hemopoiesis. They disappear completely at birth when extramedullary hemopoiesis disappears. They reappear frequently in the blood of infants and young children, an age group in which extramedullary hemopoiesis is extremely common. The degree of normoblastemia in erythroblastosis fetalis shows good parallelism to the extent of hemopoietic infiltration in the liver and other tissues. The composition of the marrow in such patients is the same whether the blood contains large numbers of normoblasts or not. If these cells come from the marrow a difference should be expected. In the severe anemias of later life in which nucleated red cells appear in the blood, extramedullary hemopoiesis is usually demonstrable at autopsy. In Mediterranean anemia, the extramedullary hemopoiesis is as characteristic of the tissues as the "immature" cell picture of the blood.

In leukemia, whether acute or chronic, widespread extramedullary infiltrations with leukemic cells are usually seen at autopsy. The

observed facts are in keeping with the theory that in leukemia, as in the other conditions mentioned, the pathologic cells appearing in the blood originate not in the marrow but at the site of the extramedullary infiltrations. The factors which determine whether in acute leukemia the blood picture shows leukopenia or leukocytosis are not completely understood. There are no significant differences in the pathologic findings between the aleukemic and the leukemic variants of the disease. Apparently then, extramedullary hemopoiesis is only one of the premises for the release of immature cells into the blood stream, and the state of cohesion or agglutination, the nature of the proliferating cells, the localization within the tissue structures and, possibly, the degree of involvement of organs other than the bone marrow may determine whether these cells appear in the circulating blood. A fair degree of correlation seems to exist [3] in the enlargement of lymph nodes, spleen and liver as determined by clinical examination on the one hand and by the height of the white blood cell count on the other. Aleukemic blood pictures are seen predominantly in patients without demonstrable enlargement of these organs, while pronounced splenomegaly, hepatomegaly and lymphadenopathy are usually, though not always, accompanied with elevated white blood cell counts with large numbers of pathologic cells in the blood stream. These observations suggest that the degree of extramedullary infiltrations is a factor in determining the white blood cell count in leukemia.

As a last example, the appearance of nucleated red cells in the blood of patients with sclerosis or fibrosis of the bone marrow may be cited. This observation cannot be explained by the process in the marrow proper but may be readily understood as a result of the concomitant myeloid metaplasia of the spleen or other organs in such patients.

Space prohibits a discussion of this extremely interesting question: Under what conditions is extramedullary hemopoiesis likely to occur? The theory concerning its role in determining the blood picture can be summarized by a direct quotation from Rohr [1]:

> . . . The presence of immature cell types in the blood does not *per se* indicate the state of the marrow but is associated with an extramedullary hemopoiesis. Myeloid reactions can occur in marrow hypoplasias and aplasias as well as in hyperplasia.

This is not the place to discuss the nature of leukemia. The question whether this condition is neoplastic or infectious is still under debate. In this, as in every other respect, it is impossible to treat the entire group of leukemias as if they were one disease. Acute and chronic leukemias must be distinguished, not on the basis of duration or of the origin of the cells, but on the basis of the behavior of the leukemic cells. In acute leukemia the cells behave as malignant elements.

3. Unpublished observations.

They are not merely immature but anaplastic and radically different from normal immature cells. By contrast, chronic myelogenous leukemia behaves more like hyperplasia: the cells are produced in increased numbers and may be immature but not necessarily anaplastic.

While acute and chronic leukemias must be differentiated, there are at present no grounds for the subdivision of acute leukemia into myelogenous and lymphatic types. Monocytic leukemia is in a class by itself and may be properly classified as an acute reticuloendotheliosis. In the ordinary acute leukemia so common in childhood adequate clinical, etiologic and hematologic grounds for a subdivision are still lacking. Since the leukemic cells are pathologic cells, they cannot be compared with normal primitive cells, myeloblasts or lymphoblasts, and mere resemblance to such cells does not justify distinctions between myelogenous or lymphatic leukemia on morphologic grounds. It remains to be seen whether such a distinction could be of clinical value. From what has been said it should be clear that the identification of leukemic cells in the acute type, and with it the diagnosis, is qualitative and not related to the immaturity of the cells per se. The appearance of immature but qualitatively normal elements in leukemia, as in other conditions, seems to depend on their presence in extramedullary sites.

In acute leukemia, the marrow is nearly always affected, and, as the normal marrow elements are suppressed, anemia, thrombopenia and a scarcity of the normal leukocytes will develop. Acute leukemia is, however, a systemic disease, and many of its features are explained by the participation of other organs. It has already been stated that the presence of leukemic cells in the blood depends on extramedullary involvement. The same is true for the immature granulocytes occasionally seen in the blood in acute leukemia and derived from normal granulocytes coexisting with leukemic cells. There is no evidence that the highly anaplastic malignant cells of acute leukemia ever mature, and the old adage "You shall know them by the company they keep" is misleading. The presence of immature granulocytes in the blood gives no information as to the origin of the leukemic cells in acute leukemia.

The nature of chronic myelogenous leukemia is completely obscure. It probably consists in a quantitative rather than qualitative aberration, and in this type which is rare in children the diagnosis does depend to a large extent on the immaturity and the increase in number of the cells in the blood.

In the discussion of leukemia as a systemic disease it was implied that the marrow is not only an organ but also part of the reticuloendothelial system and participates in the general reactions of that system just as the liver, spleen and lymph nodes play dual parts in the body. This explains the involvement of the marrow in the so-called reticuloendothelioses, such as Gaucher's disease and Niemann-Pick dis-

ease. The role of the marrow in infections, both acute and chronic, is an extremely interesting and important subject but one which involves the function of the marrow as a reticuloendothelial organ and has no direct bearing on hemopoiesis. These immunologic reactions cannot be discussed here, but they should be mentioned because of the practical diagnostic importance of marrow aspiration in infections, particularly parasitic infections such as malaria, histoplasmosis, leishmaniasis and others.

Within the framework of this discussion it was impossible to give more than a bird's-eye view of an extremely complicated subject. Many of the statements and theories presented are controversial but seemed justified in the present state of knowledge, in the hope that future research will prove or disprove them.

SUMMARY

The concepts developed in this paper may be summarized as follows:

1. The bone marrow reacts in a uniform manner to stimuli and behaves in this respect as an organ.

2. With rare exceptions, the study of aspirated marrow gives reliable information about qualitative changes. Quantitative observations properly interpreted can give valuable information regarding functional disturbances but must be evaluated with greater caution.

3. The marrow organ under normal conditions is the sole organ of hemopoiesis in postnatal life. Under pathologic conditions in infancy, less often in later childhood and adult life, extramedullary hemopoiesis can influence the blood picture and must be considered in the interpretation of bone marrow and blood findings.

4. Hemopoiesis involves three partial functions—multiplication (mitotic division), maturation and release. Each of these functions must be intact and properly integrated. Disturbances in marrow function can result from depression of mitosis at various levels of cellular development (as in deficiency of antianemia principle) or from interference with the maturation process proper (as in iron deficiency). Disturbances of the release mechanism as such are unknown. The retention of cells in the marrow is the result of immaturity.

5. Marrow hyperplasia is not necessarily an indication of effective increase in function. It is often the result of dissociation of partial functions. The true measure of marrow function is the output of functional elements, which requires proper integration of multiplication, maturation and release. The usual stimulus for increased performance is increased demand.

6. The reactivity of the bone marrow may be defined as the ability to respond optimally to graded stimuli. The reserve power of the marrow is determined not only by the anatomic size of the organ but by the degree to which its function can be intensified.

7. There is considerable evidence that the appearance of immature or primitive cells in the blood is not accounted for by a pathologic release mechanism from the marrow but by extramedullary hemopoiesis.

8. Even though it biologically behaves as an organ, the bone marrow is also a part of the reticuloendothelial system and participates in its systemic reactions. Leukemia, Gaucher's disease and many infections may be considered as systemic diseases involving the reticuloendothelial system.

9. Leukemia is an irreversible systemic disease. Acute and chronic leukemia must be distinguished not on the basis of duration but on the basis of the biologic behavior of the leukemic elements. Acute leukemia behaves like a neoplasia with proliferation of malignant anaplastic cells, rather than merely immature ones. The diagnosis is largely a qualitative procedure. At present there is no etiologic, clinical or morphologic basis for a distinction between acute myelogenous and lymphatic leukemia. In chronic leukemia the changes in the marrow organ and in the blood are essentially quantitative.

5224 St. Antoine Street (2).

RETICULOGRANULOMA

Report of a Case of Eosinophilic Granuloma of Bone Associated with Nonlipid Reticulosis of Skin and Oral Mucosa Under the Clinical Picture of Hand-Schüller-Christian Disease

HERMANN PINKUS, M.D.
MONROE, MICH.
AND
LYMAN A. COPPS, M.D.
STANLEY CUSTER, M.D.
AND
STEPHAN EPSTEIN, M.D.
MARSHFIELD, WIS.

ONE OF the most interesting recent developments in the field of pathology is the concept, first advanced by Farber and Green,[1] that "eosinophilic granuloma of bone" is the mildest form of a group of reticuloendothelial diseases. Other members of this group of "peculiar inflammatory histiocytosis" (Jaffe and Lichtenstein[2]) are Hand-Schüller-Christian and Letterer-Siwe diseases. If this concept is correct, it was to be expected that cases of eosinophilic granuloma would be observed in which other organs besides the bones are affected.

The first case of this kind was published by Curtis and Cawley.[3] Their patient was a 2 year old girl who had cutaneous manifestations of specific character, in addition to multiple involvement of bones. The case which forms the basis of our report was seen at the Marshfield Clinic in January 1946 and was diagnosed clinically as Schüller-Christian disease. Tissue sections of the bone lesion, however, were interpreted as lymphosarcoma or myeloma, and a correct diagnosis was made only after one of us (H. P.) had had occasion to examine the sections of Curtis and Cawley's case.

From the Laboratory of Dermopathology of Monroe Hospital, Monroe, Mich., and the Department of Dermatology, Wayne University Medical College, Detroit, (Dr. Pinkus) and the Marshfield Clinic and St. Joseph's Hospital, Marshfield, Wis. (Dr. Copps, Dr. Custer and Dr. Epstein).

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REPORT OF CASE

C. J. F., a girl 9 months of age, was brought to the clinic on Jan. 4, 1946 on account of a painful swelling above her left ear of three months' duration. Lately, the swelling had not increased in size but had become more painful. The child had become "fussy." She had had a persistent cough and nasal discharge following pneumonia in November 1945. There was no history of a draining ear. The child had a "rash" on the abdomen and scalp. The general well-being was not disturbed. The appetite was fair; there was no loss in weight.

Examination revealed a well developed and well nourished, pale child, weighing 21¾ pounds (9.9 Kg.). There was a tender, soft, fluctuant mass, poorly outlined, in the left temporo-occipital region, just posterior to the mastoid process, measuring about 5 by 6 cm. The left auditory canal was narrowed and the tympanic membrane bulging. The right ear was normal. The tonsils were large and subacutely inflamed.

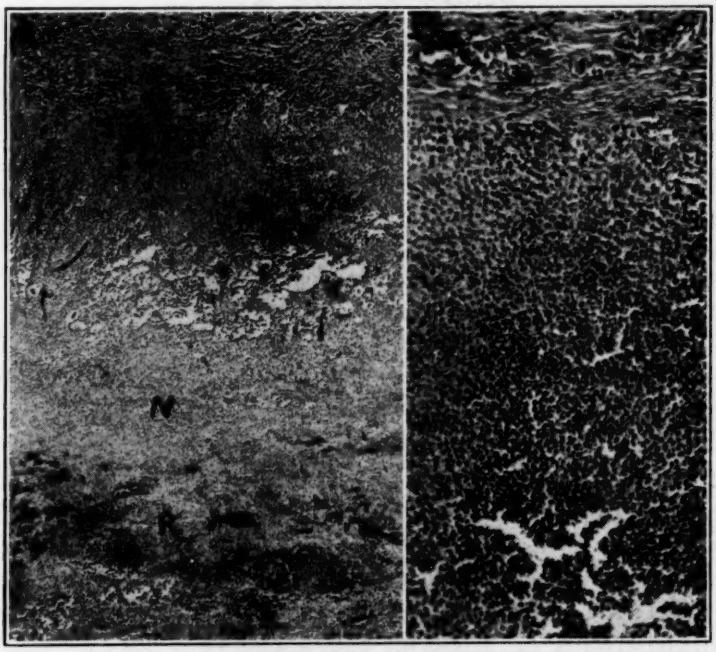

Fig. 1.—Eosinophilic granuloma of skull; hematoxylin and eosin. *A*, low power view showing, from top to bottom: periosteal fibrous tissue; zone of tumor-like granulomatous infiltrate containing accumulations of eosinophils (*E*) and lymphocytes (*L*); zone of necrosis (*N*), and massive hemorrhage (*R*). *B*, high power view of the invasive border zone showing the solid arrangement of the large pale cells. Erythrocytes and eosinophilic granulocytes appear as small black dots.

The scalp was covered with a scaly dermatitis composed of small papules, some of which were surrounded by an inflammatory areola. Most of them showed yellowish scales resembling seborrheic dermatitis. Similar lesions were scattered over the lower part of the chest and abdomen, both anteriorly and posteriorly.

Results of physical examination otherwise were essentially normal except for loud tubular rales heard bilaterally over the upper part of the chest. The liver and spleen were within normal limits. No enlarged lymph nodes or other masess were found.

Roentgenographic examination of the skull revealed a single, irregularly shaped defect with fairly sharp outlines, about 2 cm. in diameter, above and posterior to the left auditory canal. No other bone lesions were present at that time.

Laboratory Data.—The hemoglobin concentration was 12.5 Gm. per hundred cubic centimeters; erythrocytes numbered 4,300,000 and leukocytes 14,000, of which 29 per cent were polymorphonuclear, 68 per cent lymphocytes and 3 per cent monocytes. Later, the differential count was normal. The total number of leukocytes varied between 11,700 and 15,100. Urinalysis of a noncatheterized specimen revealed 30 mg. of albumin and pus microscopically.

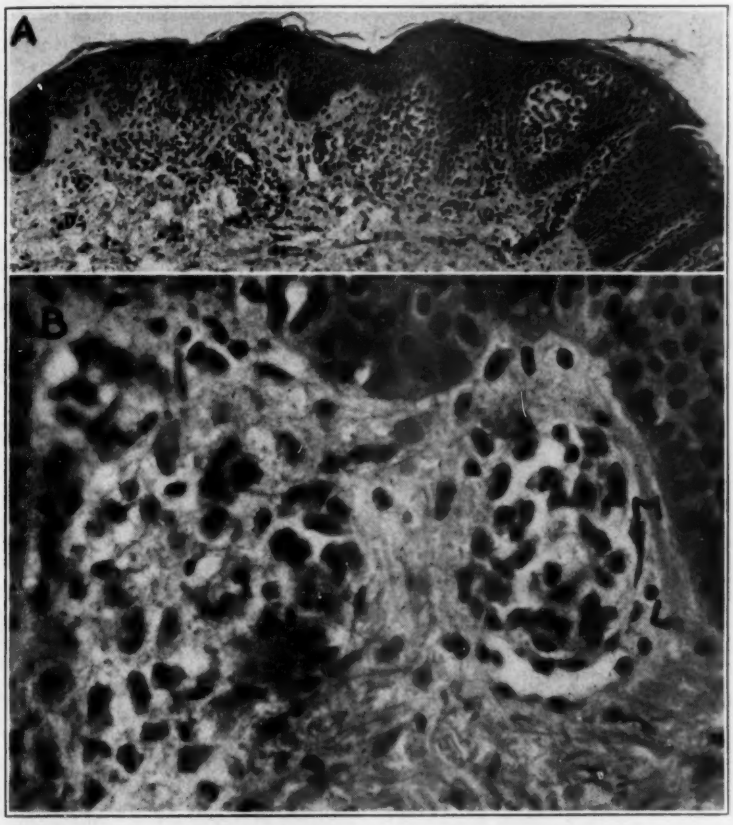

Fig. 2.—Small cutaneous papule. *A*, low power view of a section stained with hematoxylin and eosin, showing the loose, mainly perivascular, arrangement of the large cells which invade the epidermis in the right half of the section. *B*, high power view of a section stained with acid orcein and Giemsa solution, showing details of the large cells, particularly several kidney-shaped nuclei. The cell just above (*L*) is a small lymphocyte. The cell just below (*M*) is a mast cell.

The child was operated on January 8, and a flat mass 5 cm. in diameter and 0.5 cm. thick was removed from the skull at the site of the swelling. An erosion of the bone was found, measuring about 4 cm. in diameter and extending through both tables and exposing the dura. Cultures taken from the mass yielded no pathogens. Microscopic examination of the tumor showed the following changes in the bone:

Two sections, 2 by 1 cm., stained with hematoxylin and eosin, showed complete replacement of the bone and periosteum by tumor-like cellular tissue which invaded

the surrounding fibrous tissue. The center of the section showed necrosis and old and fresh hemorrhage, and also a small area of calcified necrotic bone. The necrotic zone contained some granulocytes, macrophages carrying debris and a few multinucleated giant cells of foreign body type. No foam cells were present. The peripheral living zone consisted predominantly of uniform large cells having nuclei up to twice the size of a red blood cell and considerable amphophilic protoplasm. The nuclei were round, oval, folded or kidney shaped and had a distinct nuclear membrane and small accumulations of chromatin without a distinct nucleolus. Some mitotic figures were present. The cells formed dense, epithelium-like aggregates, or were more loosely arranged and connected to each other by protoplasmic processes or were completely rounded off and separated. They

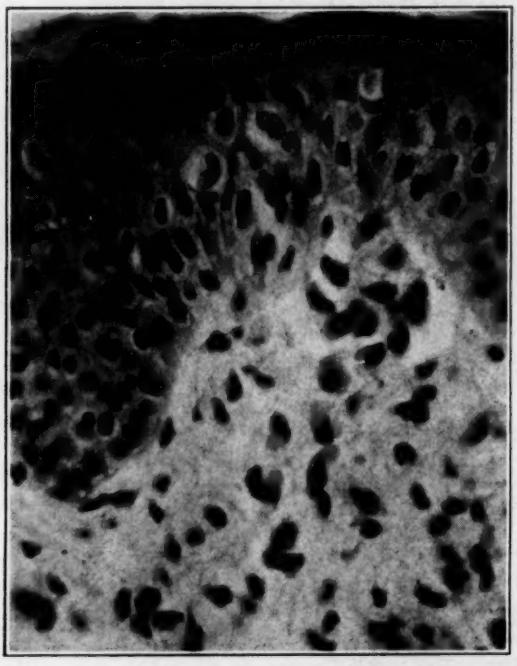

Fig. 3.—Small cutaneous papule. Section stained with hematoxylin and eosin, illustrating the unusual feature of histiocytes invading the epidermis.

accumulated particularly around numerous blood vessels which were lined by a distinct row of endothelium but had no media. The pathologic cells followed the blood vessels into the surrounding fibrous tissue. In addition to these cells, which had the characteristics of reticulum cells and histiocytes, there were accumulations of lymphocytes and particularly numerous eosinophilic granulocytes which formed large clumps and were also seen singly between the large cells. The tumor was diagnosed microscopically first as a reticulum cell lymphosarcoma by a competent pathologist. Such a diagnosis is understandable considering the histopathologic observations. However, after the cutaneous lesions were studied, we felt that a diagnosis of eosinophilic granuloma of bone was justified.

A cutaneous lesion from the abdomen presented the following histopathologic picture (figs. 2 and 3):

Frozen sections were stained with scarlet red and hematoxylin. Paraffin sections were stained with hematoxylin and eosin, hematoxylin and Van Gieson's mixture, acid orcein and Giemsa's mixture and impregnated with silver for reticulin fibers.

The sections were of glabrous skin and showed several areas in which large cells accumulated in the papillae and subpapillary layer. Some of the cells were seen deeper in the skin, along hair follicles and around blood vessels. These cells had characteristics similar to those found in the skull, but a higher percentage had

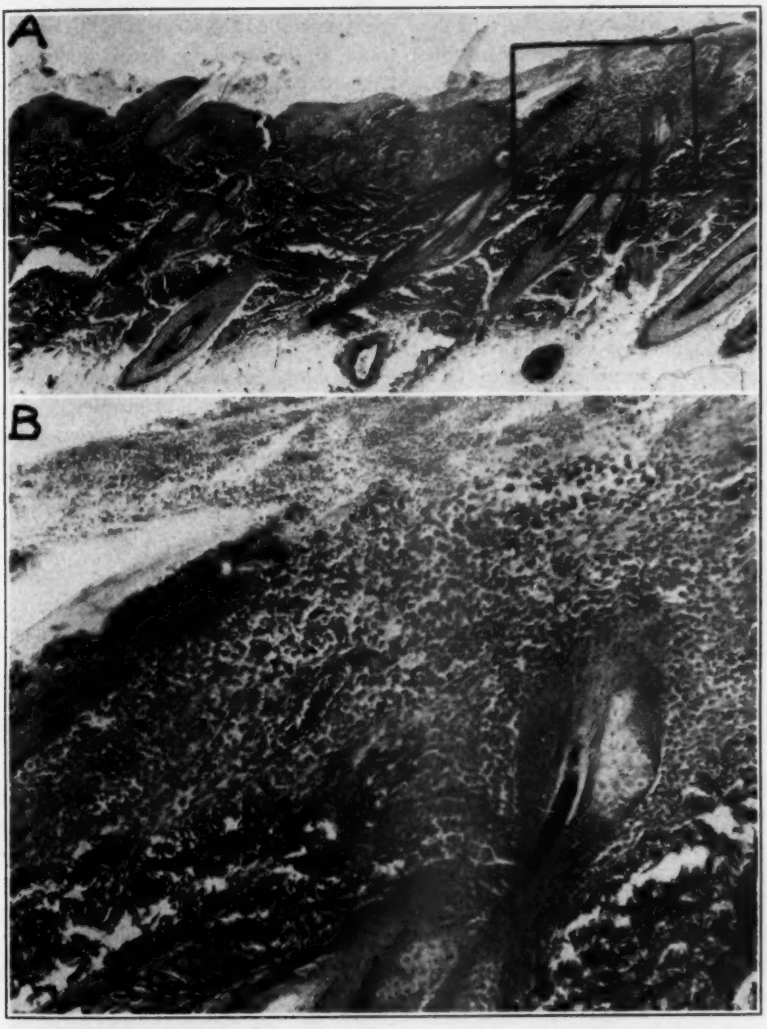

Fig. 4.—Eroded plaque of scalp; acid orcein and Giemsa solution. *A*, low power view showing normal skin at the left, destruction of the epidermis and upper layers of the corium by a dense granuloma at the right. *B*, high power view of the small outlined area of part *A*. The surface is covered with blood, the epidermis is lost except for a small island in the right upper corner, the cutaneous appendages are well preserved. The infiltrate of large pale cells has a sharp lower border. It has completely destroyed the elastic fibers, which appear as a dense black felt in the normal parts of the corium.

kidney-shaped or horseshoe-shaped nuclei, and there were no mitoses. They did not form dense aggregates except in a few papillae which they distended. Most of them were arranged around blood vessels and in lymph spaces. Some cells entered the epidermis and lay singly in small cavities or formed groups in vesicular intraepidermal spaces. The epidermis was otherwise normal. There were small areas of parakeratosis in the horny layer above the papular infiltrates. Some lymphocytes and occasional eosinophilic granulocytes and mast cells were observed in the corium. The collagenous and elastic fibers were pushed aside and thinned out by the infiltrate. A loose net of reticulum fibers enmeshed the large cells. The normal parts of the skin showed silver fibers only at the epidermodermal junction and around blood vessels. No abnormal amounts of lipid, particularly no doubly refractile substances, were present.

Course of the Disease.—Between January 21 and 29 the child received a total of 1,600 r to the left temporal area, given in fractional doses of 200 r each, at 150 kilovolts, unfiltered, at an average skin distance of 50 cm. Periodic roentgenologic examination of the skull showed continued improvement; after ten months there was no visible evidence of the bone lesion. The cutaneous eruption of the trunk was not treated.

In July the child was apparently in good health. The papular eruption had nearly disappeared from the trunk but was more pronounced on the scalp, where it presented a peculiar picture. There were pinhead-sized, yellowish keratotic lesions which did not come off easily. They were grouped into plaques of about 2 by 3 cm. containing from six to ten of these lesions. They were surrounded by a somewhat dirty looking superficial scale. A biopsy from one of these lesions (Jan. 25, 1947) revealed the following changes (figs. 4 and 5):

The epidermis was lost over large stretches of the sections. This exposed a dense cellular infiltrate which occupied the upper third of the corium and was sharply demarcated below. The infiltration consisted almost entirely of the same type of large cells seen in the other specimens, with a sprinkling of lymphocytes and eosinophilic granulocytes. It had entirely replaced the normal collagenous and elastic tissue and was supported by a loose network of reticulin fibers. The hairs of the scalp and the cutaneous glands were well preserved and traversed the layer of infiltration. In those areas of the sections where the epidermis was present, one could see small accumulations of the large cells around the subpapillary vessels. As the infiltrations enlarged they became confluent, encroached on the epidermis from below, destroyed collagenous and elastic tissue and formed a network of reticulin fibers which were absent in the normal tissue except around blood vessels and at the epitheliomesodermal junction. Frozen sections showed occasional fine droplets of lipid in histiocytes, but no foam cells.

In September a swelling of the roof of the mouth was noted. This turned gradually into an ulcerative destructive lesion with loss of several teeth. The lesions were treated with roentgen rays. To each side of the face 450 r were given in fractional doses of 150 r. There was a slow response.

On Jan. 25, 1947, a biopsy was taken from the lesion of the palate which revealed the following picture (figs. 6 and 7):

The sections consisted of gingival tissue and included part of the alveolar lining, as well as the buccal surface of the gums. The gingival epithelium showed some edema and transmigration of leukocytes. It ended abruptly at the alveolar margin. Beneath the epithelium, and separated from it by a narrow zone of fairly normal connective tissue, was a granulomatous infiltrate which also formed the alveolar lining. This granuloma was visible particularly in silver-impregnated

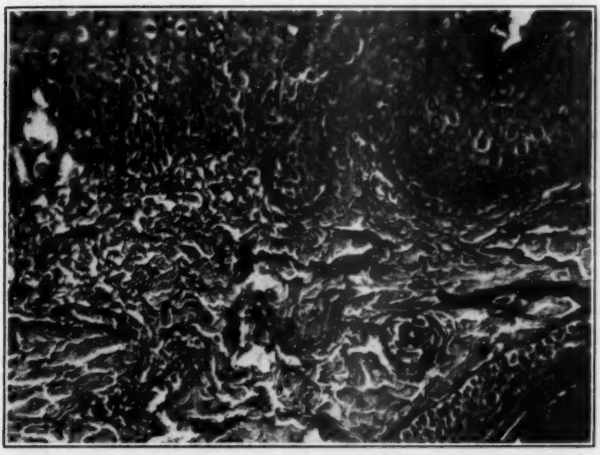

Fig. 5.—Plaque of scalp, section impregnated with silver according to Wilder's modification. An area to the left of the main lesion is shown. There is a small accumulation of large cells in the left half of the picture, normal epidermis, corium, cross section of a sweat duct and part of a hair follicle in the right half. The normal felt of short reticulin fibers appears as a sharp black line at the border between epithelium and connective tissue. The large cells are spun in with a network of newly formed black fibers which also follow a small blood vessel down into the corium.

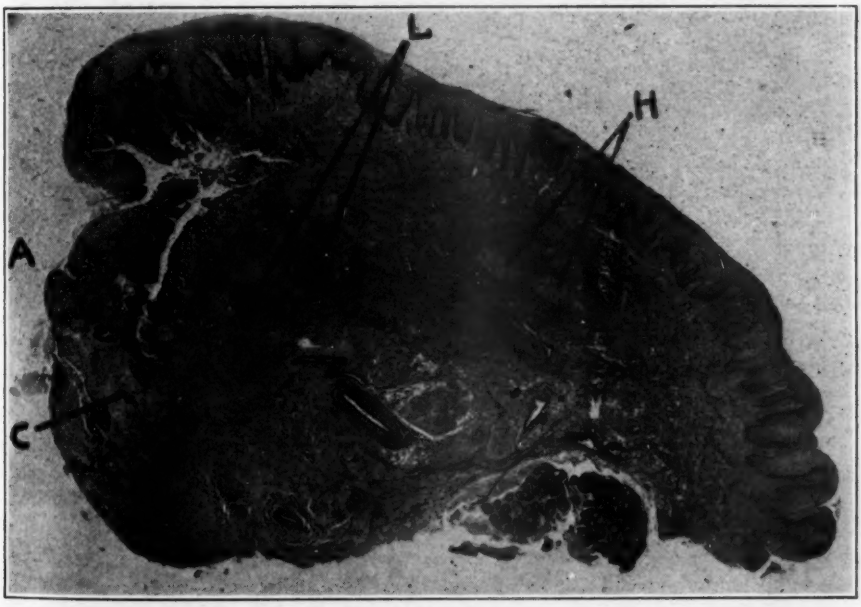

Fig. 6.—Eosinophilic granuloma of gingiva, acid orcein and Giemsa solution. Alveolar margin is seen at the left (*A*), epithelium of the gingiva at the right. Granuloma forms a semicircular zone around the large artery-vein-nerve complex. There is an accumulation of large pale-staining histiocytes (*H*) and of small and large lymphocytes (*L*). The stroma is formed by chromophobic connective tissue which consists of a dense felt of reticulin fibers and is well visible as the light area at *C*. The dark stippling in the lower left corner and around the islands of histiocytes (*H*) is due to masses of eosinophils.

sections because the cells were embedded in a dense felt of reticulin fibers which formed a semicircular zone around the deep artery-vein-nerve complex of the gingiva. The granuloma was fairly vascular and consisted of a mixture of histiocytes, lymphocytes, plasma cells, mast cells and eosinophilic granulocytes. The lymphocytes formed some dense nodes which resembled lymph follicles because of their germinal centers. The histiocytes were partly scattered, particularly near the alveola where there were numerous macrophages, foam cells and some neutrophilic leukocytes. In other places they formed small or larger islands which were free from reticulin fibers. The eosinophils were scattered throughout, accumulated in some areas in masses which were visible under low magnification, and near

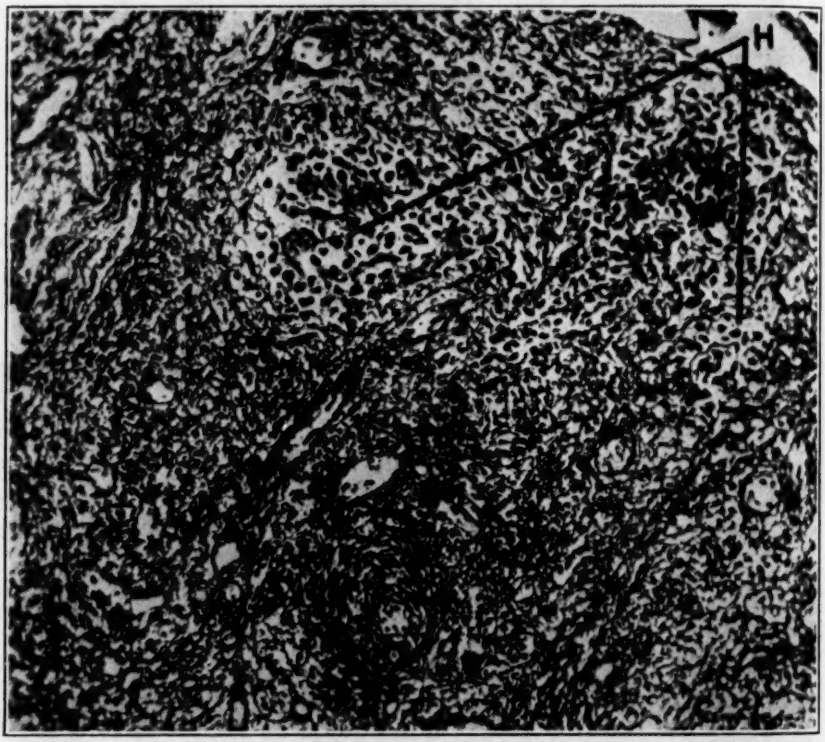

Fig. 7.—Eosinophilic granuloma of gingiva; section impregnated with silver according to Wilder's modification. Argyrophilic fibers form a dense stroma except where large histiocytes accumulate (*H*).

the alveola they disintegrated leaving masses of free eosinophilic granules behind. Frozen sections showed practically no lipid.

At that time an infiltrated ulcer of the right labium majus was noted, measuring about 2 cm. in diameter. It had a slightly necrotic center. The cutaneous lesions, as well as the ulcer of the vulva, responded satisfactorily to moderate fractional doses of roentgen rays, and the lesions of the mouth were also healing, following an additional roentgen course totaling 1,100 r.

In July 1947 the child had pain in the left arm. Roentgenologic examination revealed a granuloma in the shaft of the humerus which is now receiving roentgen ray therapy. In October 1947 the child was in excellent general health. At the present time (January 1949) the child continues in good health. No new bone

lesions have appeared, but there has been a recurrence of the ulcer of the right labium majus which is responding again satisfactorily to roentgen therapy.

COMMENT

What is now generally called eosinophilic granuloma of bone was first described correctly by Otani and Ehrlich [4] and Lichtenstein and Jaffe [5] who wrote on the subject independently in 1940. Lichtenstein and Jaffe coined the name eosinophilic granuloma of bone. Since then, a considerable number of cases has been described, and the number of publications is increasing. Recently, *The Journal of the American Medical Association* [6] stressed the points that the lesions are benign and that they are restricted to bones.

Cutaneous lesions, on the other hand, are more or less commonly found in the other two members of this group of reticuloendothelial diseases. According to Sundelius,[7] who analyzed 63 cases of Hand-Schüller-Christian disease, cutaneous lesions were seen in 29 (46 per cent) and were the initial sign in 6 (11 per cent). Cases of Letterer-Siwe disease present some kind of cutaneous lesions in almost every instance. The lesions in this acute and usually rapidly fatal disease are most frequently described as purpura, occasionally as a papular rash, or as crusty eczema clinically resembling seborrheic dermatitis. Unfortunately, few observers examined the skin microscopically, even at autopsy. Those who did almost invariably reported specific cellular infiltrates.[8] Cutaneous manifestations in Hand-Schüller-Christian disease may be of several different types (Lane and Smith [9]). General

4. Otani, S., and Ehrlich, J. C.: Solitary Granuloma of Bone Simulating Primary Neoplasm, Am. J. Path. **16**:479-490, 1940.

5. Lichtenstein, L., and Jaffe, H. L.: Eosinophilic Granuloma of Bone, with Report of a Case, Am. J. Path. **16**:595-604, 1940.

6. Eosinophilic Granuloma of Bone, Current Comment, J. A. M. A. **133**:1284 (April 26) 1947.

7. Sundelius, H.: Zur Kenntnis der Lipoidosen, speziell vom Typus Schüller-Christian, Acta med. Scandinav. **87**:402-441, 1936.

8. (*a*) Letterer, E.: Aleukämische Retikulose, Frankurt. Ztschr. f. Path. **30**:377-394, 1924. (*b*) Roussy, G., and Oberling, C.: Akute, wahrscheinlich infektiöse aleukämische Retikulose bei einem Säugling, Wien. med. Wchnschr. **84**:407-413, 1934. (*c*) Foot, N. C., and Olcott, C. T.: Report of a Case of Non-Lipoid Histiocytosis (Reticuloendotheliosis) with Autopsy, Am. J. Path. **10**: 81-96, 1934. (*d*) Glanzmann, E.: Infektiöse Retikuloendotheliose (Abt-Letterer-Siwe'sche Krankheit) und ihre Beziehungen zum Morbus Schüller-Christian, Ann. pædiat. **155**:1-8, 1940. (*e*) Wallgren, A.: Systemic Reticuloendothelial Granuloma: Nonlipoid Reticuloendotheliosis and Schüller-Christian Disease, Am. J. Dis. Child. **60**:471-500 (Sept.) 1940.

9. Lane, C. W., and Smith, M. G.: Cutaneous Manifestations of Chronic (Idiopathic) Lipoidosis (Hand-Schüller-Christian Disease): Report of Four Cases, Including Autopsy Observations, Arch. Dermat. & Syph. **39**:617-644 (April) 1939.

pigmentation or bronzing have been described, as well as typical xanthelasmas of the eyelids and xanthomatous lesions of the scalp. Occasionally, the cranial lesions break through the overlying skin and cause granulomatous ulcers. The diagnosis may be established by biopsy of the cutaneous ulcers (Herzau and Pinkus[10]). The most frequent lesion is a clinically quite characteristic exanthem which consists of small yellow or brown macules and papules which at times may have a purpuric component. Histologically, these lesions often represent minute xanthomas with typical foam cells, but in other cases no lipid is found and the infiltrate consists of large histiocytes. In these cases the lesions are histologically indistinguishable from those of Letterer-Siwe disease, particularly when hemorrhage is associated. Still another type of cutaneous lesion is described as eczematous and seborrheic. Even bullous and vesicular lesions have been observed.[11] Again, relatively few observers have examined these eruptions microscopically,[12] and one can only suspect that the seborrheic lesions were of a similar nature as those seen in Letterer-Siwe disease, or in Curtis and Cawley's and our case.

Before we try to interpret our case, we wish to remark about the criteria for the diagnosis of either Letterer-Siwe disease or Hand-Schüller-Christian disease.

After the interpretation of Rowland (1928),[13] Hand-Schüller-Christian disease was considered to be a primary disturbance of lipid metabolism, a xanthomatosis. Ten years later, Thannhauser and Magendantz[14] concluded that

> . . . the general assumption that essential xanthomatosis is a storage disease of the reticular cells due to a disturbance of the general intermediary metabolism of cholesterol, is not in conformity with physiological and clinical findings.

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10. Herzau, W., and Pinkus, H.: Beitrag zur Schüller-Christianschen Krankheit, Klin. Monatsbl. f. Augenh. **89**:721-729, 1932.

11. Lane and Smith,[9] case 1. Andrews, G. C., in discussion on Lane and Smith.[9]

12. Merritt, K. K., and Paige, B. H.: Xanthomatosis (Schüller-Christian Syndrome): Report of a Case with Necropsy, Am. J. Dis. Child. **46**: 1368-1392 (Dec.) 1933. Lichty, D. E.: Lipoids and Lipoid Diseases: II. Xanthomatosis (Schüller-Christian's Type), Arch. Int. Med. **53**:379-390 (March) 1934. Lane and Smith.[9] Hamblen, E. C.; Arena, J. M., and Cuyler, W. K.: Hand-Schüller-Christian Disease: Report of a Case in Which Urinary Androgens Were Titrated, Am. J. Dis. Child. **60**:352-358 (Aug.) 1940.

13. Rowland, R. S.: Xanthomatosis and the Reticulo-Endothelial System: Correlation of an Unidentified Group of Cases Described as Defects in Membranous Bones, Exopthalmos and Diabetes Insipidus (Christian's Syndrome), Arch. Int. Med. **42**:611-674 (Nov.) 1928.

14. Thannhauser, S. J., and Magendantz, H.: The Different Clinical Groups of Xanthomatous Diseases: A Clinical Physiological Study of Twenty-Two Cases, Ann. Int. Med. **11**:1662-1746, 1938.

They classified cases of Hand-Schüller-Christian type in their "normocholesteremic" group and suggested

> . . . that essential xanthomatosis is a cellular disease of reticulum cells caused by an intracellular disorder of their cholesterol metabolism.

This view opens the interesting possibility that the xanthomatous derangement of cellular metabolism may occur in cells which for any reason have accumulated in abnormal numbers or are otherwise diseased. Meanwhile, more and more cases had been found which indicated that lipid deposits are secondary, and that the lesions are primary destructive granulomas composed mainly of reticulum cells and histiocytes.[15] Hand-Schüller-Christian disease provides one of the instances in which the names of some early authors were tacked on a group of cases, the nature of which was not too well understood. Originally, the name designated the triad of exophthalmos, diabetes insipidus and granulomatous defects in the skull. Gradually, the basis for diagnosis shifted from the clinical to the pathologic side, until now many cases are described under this designation which present few or none of the original signs (Henschen[16]). The name, as it is now used, covers such a variety of cases that it threatens to become too vague. Now that the disease has been put into another category, it may be advisable to restrict the term Hand-Schüller-Christian disease to the original triad which these authors described, and to accept a more significant name, such as "lipid granulomatosis" (Chester[17]), for those cases of reticuloendothelial granulomas in which presence of lipids, specifically of cholesterol and its esters, is the predominant feature.

The cases of Letterer-Siwe disease, also called nonlipid reticuloendotheliosis or histiocytosis, while presenting a colorful array of varying signs and symptoms, appear to be a fairly well defined group in which the disease condition assumes a malignant, systematized character. The rapidly fatal course appears to prevent the xanthomatous transformation of the granulomatous tissue (Wallgren[8e]).

Transitional cases between the nonlipid and lipid varieties have been described; they showed an acute onset but had a more protracted

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15. Ceelen, W.: Ueber die Lipoidgranulomatose (Hand-Schüller-Christiansche Krankheit), Deutsche med. Wchnschr. **59**:680-681, 1933. Gerstel, G.: Ueber die Hand-Schüller-Christiansche Krankheit auf Grund gänzlicher Durchuntersuchung des Knochengerüstes, Virchows Arch. f. path. Anat. **294**:278-303, 1934. Wätjen, J.: Beitrag zur Kenntnis des Morbus Schüller-Christian, Beitr. z. path. Anat. u. z. allg. Path. **96**:443-465, 1936. Wallgren.[8e]

16. Henschen, F.: Ueber Christians Syndrom und dessen Beziehungen zur allgemeinen Xanthomatose, Acta pædiat. (supp. 6) **12**:1-93, 1931.

17. Chester, W.: Ueber Lipoidgranulomatose, Virchows Arch. f. path. Anat. **279**:561-602, 1931. Chester, W., and Kugel, V. H.: Lipoidgranulomatosis (Type, Hand-Schüller-Christian): Report of a Case, Arch. Path. **14**:595-612 (Nov.) 1932.

course and ended in lipid granulomatosis (Jaffe and Lichtenstein [2]). On the other side, Engelbreth-Holm, Teilum and Christensen [18] presented 5 cases which formed a continuous series from the solitary eosinophilic granuloma of bone over multiple lesions to the full blown picture of Hand-Schüller-Christian syndrome. The authors concluded that eosinophilic granuloma of bone is a monosymptomatic form of lipid granulomatosis which often heals without becoming systematized. Jaffe and Lichtenstein [2] described the case of a girl whose first symptom was a destructive lesion of the radius which histologically was eosinophilic granuloma. But she later died with all the manifestations of Letterer-Siwe disease, including cutaneous lesions. Theirs really was the first detailed description of a case in which eosinophilic granuloma of bone and specific cutaneous lesions were observed in the same patient.

Curtis and Cawley's case [3] is different and of great importance insofar as the patient presented extensive cutaneous lesions of unique type as the first manifestation. The bony defects were discovered only by roentgenologic examination and apparently never caused symptoms. With the exception of a few small, nontender lymph nodes, no evidence of systemic involvement was found. The lesions cleared under roentgen ray treatment, and the patient, who was 8 months old at the onset of the disease, has remained in good general health through more than three years. The bony lesions responded to roentgen ray therapy in the manner characteristic of eosinophilic granulomas. The cutaneous lesions were described as small red discrete and coalescent papules and as weeping granulomatous patches. In addition, there was a scaly eruption on the scalp similar to seborrheic dermatitis. There were also small grayish white macules on the oral mucosa. Histologic examination of the papular cutaneous lesions, as well as of the unique granulomatous plaques, showed a uniform picture entirely analogous to that seen in typical eosinophilic granuloma of bone.

Our case showed a still different combination of manifestations. The original bone tumor was a typical solitary granulomatous lesion composed of reticulum cells and containing a high percentage of eosinophils. No frozen sections were made, but the paraffin sections showed no foam cells. The lesion healed completely after surgical removal and roentgen ray treatment. At the same time, however, the baby, who was in good general health, showed a wide distribution of small accumulations of reticulum cells in the skin, here without the association of eosinophils. The papules contained no lipid, and in this respect differed from the papular xanthomas of lipid granulomatosis.

18. Engelbreth-Holm, J.; Teilum, G., and Christensen, E.: Eosinophil Granuloma of Bone—Schüller-Christian's Disease, Acta med. Scandinav. **118**:292-312, 1944.

They corresponded to the histologic description given by Roussy and Oberling [8b] of a similar eruption in Letterer-Siwe disease. Clinically, the eruption resembled that observed in lipid granulomatosis, and it has been mentioned previously that cutaneous lesions in this type do not always contain lipid.

Later, patchy lesions developed on the scalp which, under the microscope, presented changes very similar to those in Curtis and Cawley's case. There were a uniform infiltration of reticulum cells and many eosinophils. Also, granulomatous lesions of the gums developed, apparently associated with destruction of bone, as several molars were discovered to be loose. Histologically, the changes again were those of eosinophilic reticulum cell granuloma without lipid.

One of the surprising features of our case, as well as that of Curtis and Cawley, was the relatively benign course of the disease. It has been pointed out repeatedly [19] that age appears to have a definite relation to the course of the disease. The younger the patient, the more rapidly downhill the course. Our baby is definitely in the age group for Letterer-Siwe disease but has survived now for three years. Enlargement of liver and spleen and other signs of systemic involvement have been notably absent. Curtis and Cawley's patient is in good health more than three years after the onset of the disease.

Another point made by several authors [18] is that if patients with Letterer-Siwe disease survive for a longer time then secondary xanthomatous changes develop. So far, this has not happened in either case, but of course it may occur in the future.

In conclusion, our case is a strong argument for the relationship of the three reticuloendothelial diseases—eosinophilic granuloma of bone, Letterer-Siwe disease and lipid granulomatosis—and lends support, if such is needed, to the concept that they are but different manifestations of the same basic process. This "unitarian" concept already has become so firmly established that the names of the three manifestations are used almost interchangeably. In particular some authors described as eosinophilic granuloma cases which far surpass the original concept while others wanted to apply the name Hand-Schüller-Christian to the entire group. It appears timely to point out that little is gained by doing so. Not only are there important differences in the pathologic processes, but the clinical picture, prognosis and therapy are so vastly different in a case of self-limited solitary bone cyst, one of progressive crippling lipid granulomatosis and one of rapidly fatal systematized reticulosis that confusion is likely to result from applying the name of one to an example of the other.

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19. Wallgren.[8c] Mallory, T. B.: Diseases of Bone, New England J. Med. 227:955-960, 1942. Jaffe and Lichtenstein.[2]

Engelbreth-Holm, Teilum and Christensen [18] concluded, and Thannhauser [20] recently has concurred with their statements, that the histologic process of the osseous and other lesions regularly shows four phases, the proliferative, granulomatous, xanthomatous and fibrous or healing stages. The Scandinavian authors apparently were of the opinion that each lesion goes through all four stages. This, it appears from the literature, is not necessary. In the acute cases of Letterer-Siwe type, there may not be enough time for the development of the xanthomatous and fibrous phases. But also in cases of "eosinophilic granuloma" fibrosis and healing apparently may result without a xanthomatous stage. Our own case so far has shown no tendency to develop xanthomatous lesions. Why the disturbance of lipid metabolism is so often, but not always, or not always from the beginning associated with the more generalized cases of this group is one of the unexplained difficulties in this field. Here the investigations of Thannhauser and Magendantz [14] show a way. If xanthomatosis is a metabolic disorder of the reticulum cell itself rather than of the body in general, one may assume that whatever cause leads to the formation of the granulomas also predisposes the cells to a derangement of their cholesterol metabolism. This derangement may take place soon, late or never.

One point which must be discussed is the relationship between "eosinophilic granuloma of bone" and "eosinophilic granuloma of skin" and the resulting difficulties of nomenclature. When Lichtenstein and Jaffe coined the term eosinophilic granuloma for the bone lesion, the same name had been used for several years for certain granulomatous skin tumors; however, these cases had not attracted much attention in the world's literature. Either by coincidence, or because of the wide interest elicited by the osseous lesions, there have been several recent publications concerning the cutaneous disease.[21] The collection of papers in the February 1947 issue of the *Archives of Dermatology and Syphilology* was particularly informative. Weidman's [21b] classification demonstrated that the cases reported or considered as "eosinophilic

20. Thannhauser, S. J.: Eosinophilic Granuloma of Bone Synonymous with Schüller-Christian Disease, Lipid Granuloma, Essential Xanthomatosis of Normocholesteremic Type and Eosinophilic Xanthomatous Granuloma, Arch. Int. Med. **80**:283-285 (Aug.) 1947.

21. (*a*) Buley, H. M.: Eosinophil Granuloma of the Skin, J. Invest. Dermat. **7**:291-300, 1946. (*b*) Weidman, F. D.: The "Eosinophilic Granulomas" of the Skin, Arch. Dermat. & Syph. **55**:155-175 (Feb.) 1947. (*c*) Lewis, G. M., and Cormia, F. E.: Eosinophilic Granuloma: Theoretic and Practical Considerations Based on the Study of a Case, ibid. **55**:176-193 (Feb.) 1947. (*d*) Lever, W. F.: Eosinophilic Granuloma of the Skin: Its Relation to Erythema Elevatum Diutinum and Eosinophilic Granuloma of Bone; Report of a Case, ibid. **55**:194-211 (Feb.) 1947. (*e*) Dobes, W. L., and Weidman, F. D.: Granulomatous Hodgkin's Disease of the Skin with Extreme Eosinophilia (Eosinophilic Granuloma of the Skin?), ibid. **55**:212-221 (Feb.) 1947.

granuloma of skin" are a loosely connected group of rather heterogenous conditions. The only point most of these cases have in common is a preponderance of eosinophilic cells in a granulomatous lesion. There appears almost general agreement that, whatever "eosinophilic granuloma of skin" is, it has no relation to "eosinophilic granuloma of bone." The only case in which a relationship is suggested is that of Lever [21d] because of the presence of foam cells in the lesion. However it seems to us that secondary xanthomatous changes are seen so commonly in a variety of cutaneous disorders that too much weight cannot be attached to this fact.

Not only are we confronted with the awkward situation that the same term, eosinophilic granuloma, is used for unrelated lesions in different organs of the body where the cumbersome method of adding "of bone" or "of skin" may serve for differentiation, but we now have also at least 2 cases, that of Curtis and Cawley and ours, in which "eosinophilic granuloma of bone" was also associated with lesions of the skin. This adds to the confusion unless we follow Weidman's [21b] suggestion and use the term "eosinophilic granuloma" in a purely morphologic histologic sense for any granulomatous lesion which contains a high percentage of eosinophils. Such usage would correspond to the accepted use of the term "plasmoma" for any considerable accumulation of plasma cells in a pathologic section. The histologic concept of plasmoma is useful in differential diagnosis because it is known that plasma cells are regularly associated with certain diseases and not with others. However, by its use we do not imply any clinical or etiologic relationship, as plasmomas are found in disorders as widely different as syphilis and nevus syringocystadenomatosus. A similar use of the term "eosinophilic granuloma" would, of course, deprive it of any definite diagnostic significance.

It is perhaps more useful to attack the problem of classification and nomenclature from another angle.

So far, no general designation has been proposed for the entire group of reticuloendothelial diseases with which we are dealing. Jaffe and Lichtenstein [2] called the underlying process a "peculiar inflammatory histiocytosis." Thannhauser [20] recently proposed "eosinophilic xanthomatous granuloma" for the localized and systemic disorder. Wallgren [8e] spoke of "systemic reticuloendothelial granuloma" when he discussed the relationship of Hand-Schüller-Christian and Letterer-Siwe diseases. He and others pointed out the vagueness of the terms "reticulosis," "histiocytosis" and "reticuloendotheliosis." Robb-Smith [22] in his scholarly classification of diseases of lymphoid tissue defined the term "reticulosis" as

22. Robb-Smith, A. H. T.: Reticulosis and Reticulosarcoma: A Histologic Classification, J. Path. & Bact. **47**:457-480, 1938.

. . . progressive hyperplasia of reticular tissue with differentiation to one or more cell types. It is commonly systematised . . . free cellular elements may be present in the circulating blood (leukemia). Owing to the proliferation arising at many points there may be apparent "infiltration" but stromal destruction is not seen and dissemination by embolism . . . is rare.

He differentiated "reticulosis" as defined by him from the malignant lesions for which he accepted the term "reticulosarcoma" (Oberling). The criterion for true blastoma according to Robb-Smith is stromal destruction as well as infiltration. A similar definition was given by Gall and Mallory [23] for malignant lymphoma, which term is more commonly used in this country for the same group of blastomatous diseases. They defined malignant lymphoma as characterized

. . . histologically by multiplication of one or more of the elements normally preset in lymph nodes to the point of destruction of nodal architecture.

These definitions, however, are too general and would include granulomatous lesions of the type which we have been discussing, even if we give due consideration to the fact that these lesions do not involve lymph nodes mainly, or even predominantly.[24]

We should like to propose the term "reticulogranuloma" for the group of diseases with which we have been dealing in this paper. A modified short classification of the proliferative reticuloendothelial diseases would look like this:

A. *Reticulosis* (Robb-Smith): Progressive hyperplasia of reticular tissue in lymph nodes or elsewhere without stromal destruction, as defined by Robb-Smith.[22]

B. *Reticulogranuloma:* More or less discrete granulomatous lesions of various organs which infiltrate and destroy normal tissue in a manner similar to the infectious granulomas and which may heal without residue or more commonly, with fibrosis and scar formation. The predominant and characteristic cell form is the reticulum cell and its modifications: histiocytes, macrophages and foam cells.

1. Systematized, progressive type, exhibiting widespread involvement of various organs, having an acute or subacute course and usually resulting fatally (Letterer-Siwe disease, nonlipid reticulosis).

2. Lipid granulomatous type, with a chronic, usually progressive course and including cases which exhibit the Hand-Schüller-Christian syndrome, and others which do not, but in which xanthomatous transformation of the granulomas predominates. The osseous system is

23. Gall, E. A., and Mallory, T. B.: Malignant Lymphoma: A Clinico-Pathologic Study of Six Hundred and Eighteen Cases, Am. J. Path. **18**:381-429, 1942.

24. It was only after the completion of this manuscript that we obtained knowledge of P. Cazal's monograph, "La reticulose histiomonocytaire," Paris, Masson & Cie, 1946. The author combined under this designation cases of Letterer-Siwe type and the monocytic leukemias. He did not discuss lipid granulomatosis, or eosinophilic granuloma, and had no knowledge of the American literature after 1942.

the site of predilection (lipid granuloma, Hand-Schüller-Christian disease).

3. Benign localized type with solitary or multiple lesions, usually restricted to bone, but occasionally involving the skin, exhibiting tissue eosinophilia and tending to heal spontaneously or with relatively simple treatment ("eosinophilic granuloma of bone," perhaps better designated as "benign reticulogranuloma" [25]).

4. Mixed and transitional cases which combine features of two or all of the major types, either simultaneously or successively.

C. *Reticulosarcoma* (Oberling), *malignant lymphoma* (Gall and Mallory): True destructive blastomas which do not usually regress.

This classification is not intended to be complete. It tries to indicate the position of our case and similar cases in the large field of diseases of the reticuloendothelial system. Our types *B* 1 and *B* 2 were classified by Robb-Smith under the heading of "medullary reticuloses," a term which, of course, applies to lymph nodes only. He designated them as reticulum-celled reticulosis and storage reticulum-celled reticulosis, respectively. For the reasons mentioned, it appears better to stress the granulomatous character of these diseases. Whether Hodgkin's disease (lymphadenoma, lymphogranulomatosis) may advantageously be classified with the reticulogranulomas is a question outside the scope of this paper.

Our case of reticulogranuloma would have to be classified under 4, as a mixed form combining the features of 3 with cutaneous lesions as they are usually seen in 1 and 2.

SUMMARY

A case of reticulogranuloma is reported in which the bony lesions of eosinophilic granuloma of bone were associated with nonlipid cutaneous lesions as they are usually observed in Hand-Schüller-Christian disease and Letterer-Siwe disease.

The relationship among these diseases is discussed, and the term "reticulogranuloma" is proposed for the whole group.

A classification of reticuloendothelial diseases is suggested.

12 East Fourth Street (Dr. Pinkus).

Marshfield Clinic (Dr. Copps, Dr. Custer, Dr. Epstein).

25. This term appears to conform to the rules of pathologic nomenclature as the reticulum cell or histiocyte rather than the eosinophil is the pathognomonic cell. Granuloma infers that the lesion is destructive, and "benign" differentiates it from the other types of reticulogranuloma, as well as from true tumors which come into roentgenologic, clinical or histologic differential diagnosis.

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

REACTIONS TO ANTIPNEUMOCOCCAL RABBIT SERUM: II. FAILURE TO ADSORB SENSITIZING ANTIBODY BY KIESELGUHR, FULLERS' EARTH, BERKEFELD FILTRATIONS, AND ALUMINUM HYDROXIDE. OSCAR SWINEFORD JR., J. Allergy **17**:187 (July) 1946.

The anaphylactic antibody was not adsorbed demonstrably from antipneumococcus serum by Fullers' earth (an impure aluminum silicate), *Kieselguhr,* multiple Berkefeld filtration or aluminum hydroxide. This is in contrast with the reported adsorption of the *E-E* (erythematous-edematous) reaction factor from a variety of antiserums by these substances.

It is of some importance that the possible identity of the *E-E* reaction and local reversed passive anaphylaxis be proved or disproved. Foshay claimed that predisposition to anaphylaxis from antiserums (other than antipneumococcus serum) does not result from the presence of the *E-E* reaction. There is evidence to suggest that an excess of specific polysaccharide does predispose to anaphylaxis from antipneumococcus rabbit serum.

FROM THE AUTHOR'S SUMMARY.

THE POSSIBLE RELATIONSHIP OF THE PLEUROPNEUMONIA-LIKE ORGANISMS TO REITER'S DISEASE, RHEUMATOID ARTHRITIS AND ULCERATIVE COLITIS. ROBERT WALLERSTEIN, BERT VALLEE and LOUIS TURNER, J. Infect. Dis. **79**: 134 (Sept.-Oct.) 1946.

A series of agglutinations were carried out on the serums of 102 patients for titers against one strain of pleuropneumonia-like organisms.

Four significant titers were obtained from patients, each of whom had various combinations of colitis, arthritis, conjunctivitis, urethritis or cervicitis and cutaneous lesions. Two of these 4 patients had the characteristic triad of arthritis, conjunctivitis and urethritis that justified a tentative diagnosis of Reiter's syndrome.

The possible relationship of these organisms to rheumatoid arthritis, chronic ulcerative colitis and Reiter's syndrome is discussed and the literature on the subject reviewed.

TOOMEY, Cleveland.

A PRESUMPTIVE MEDIUM FOR DIFFERENTIATING PARACOLON FROM SALMONELLA CULTURES. MARTHA L. CHILTON and MACDONALD FULTON, J. Lab. & Clin. Med. **31**:824 (July) 1946.

The authors describe a new multiple carbohydrate medium which differentiates paracolon bacilli as a group from Salmonella organisms. The medium contains 0.5 per cent each of adonitol, esculin, salicin and sucrose. It serves as a rapid means of differentiating paracolon from Salmonella cultures on the basis of fermentation of one or more of the four carbohydrates by paracolon bacilli but not by Salmonella.

WILKINSON, Galveston, Texas.

Metabolism; Infant Feeding; Milk and Other Foods

DOES MILK BETWEEN MEALS HAMPER THE APPETITE OR FOOD INTAKE OF THE CHILD? IRVING J. WOLMAN, J. Pediat. **28**:703 (June) 1946.

For nearly five months, 59 convalescent children in a rest home for rheumatic fever patients were given a 7 ounce (210 cc.) glass of milk twice daily, one hour

before meals, homogenized and pasteurized milk being served in alternate months. These before-meal feedings failed to elicit in any child undesirable symptoms of anorexia, gastrointestinal distress or decreased consumption of food attributable to either type of milk.

Eighteen of these children were later subjected to a more quantitative three week study of diet and food intake. Extra milk, either pasteurized or homogenized, was given in 7 ounce quantities three times a day, one hour before each meal, for two of the three weeks, and the amounts of food taken spontaneously during mealtimes were carefully measured. It was observed that the amounts taken at mealtimes of calories, minerals, protein and all other nutrients were approximately equal in the control week and the two weeks in which milk, whether pasteurized or homogenized, was fed before meals. The added milk proved a true dietary supplement and was well taken. The two forms appeared to be equally well metabolized.

No evidence was seen in these experiments to warrant one in advising the child's discontinuing the taking of milk between meals. The data indicated, on the contrary, that it is wise to make available such extra servings whenever there is need of improving a child's nutritional status or food intake.

FROM THE AUTHOR'S ABSTRACT.

BLOOD TRANSFUSIONS IN TREATMENT OF ALIMENTARY DYSTROPHIES IN CHILDREN. U. S. KUCHER, Pediatria **52**:41 (April) 1944.

The author reports his results with blood transfusions in the treatment of 86 children with severe alimentary dystrophy. A total of 291 transfusions, or an average of 3 transfusions per child, was given. The transfusion methods used for infants and older children are described. Unfavorable results were obtained with this treatment in the severe cases of alimentary dystrophy. Favorable results were obtained with transfusions in moderately severe cases of the condition, especially in older children and in those with the complication of an infectious process, such as dysentery and whooping cough. Here repeated transfusions improved the child's appetite, the state of immunity and the secondary anemia. The author's conclusions are as follows: Blood transfusions are definitely indicated in moderately severe forms of alimentary dystrophy with edema or diarrhea. Transfusions are contraindicated in alimentary dystrophy with extensive generalized edema, severe polyavitaminosis and signs of renal irritation, especially in young children.

BODER, Los Angeles.

ORAL AND INTRAVENOUS ADMINISTRATION OF AMINO ACIDS. G. PASQUINUCCI, Riv. clin. pediat. **44**:573 (Sept.) 1946.

Pasquinucci reviews the American literature on the oral and parenteral administration of the amino acids.

HIGGINS, Boston.

NOURISHMENT OF NEWBORN INFANTS, WITH SPECIAL REFERENCE TO PREMATURE BABIES. V. MORF, Ann. pædiat. **168**:40 (Jan.) 1947.

In a comparison of mixed feedings of sucklings, between that with breast milk and buttermilk and that with breast milk and dried protein milk (with two thirds of its fat content removed), the following results were obtained: The infants did well with both kinds of food, but the results were better with breast milk and dried protein milk. The children were less inclined to be sick or to bring up some of their food; their stools were better on the whole, and their average daily gain was 7.5 Gm. greater than that of the group which received breast milk and buttermilk.

The indication to feed newborn babies on breast milk and dried protein milk is a tendency to loose stools. On perfectly healthy premature babies, the addition of dried protein milk exerts a beneficial influence.

The high energy quotient of premature babies and the necessity of feeding them a formula of a higher calorific value than that given full term babies are emphasized.

FROM THE AUTHOR'S SUMMARY.

Vitamins; Avitaminosis

HYPOVITAMINOSIS A IN SCHOOL CHILDREN IN ROME IN RELATION TO WAR DIETS. R. DELLA CASA and A. GRIGNOLO, Arch. ital. di pediat. e puericolt. **11**:301, 1946.

In order to verify the damage suffered by the children in Rome in the last war period, the authors examined school boys for possible symptoms of vitamin A deficiency and established its connection with the food supply during the war.

They studied the dark adaptation, the condition of the eye and its adnexa, the somatic development and the general status of the other body systems, particularly the epithelium, in 239 children between 6 and 15 years of age. Only those who showed improvement in dark adaptation after treatment with vitamin A preparations were considered deficient in the vitamin.

The authors concluded that at the end of the period November 1944 to May 1945, 45.2 per cent of the children examined showed vitamin A deficiency. The connection between this condition and general nutritional deficiency was clear. The histories of the patients showed that during the aforementioned period the vitamin A supply was less than the normal requirement for 71.4 per cent of the children.

FROM THE AUTHORS' ABSTRACT.

EXPERIMENTAL STUDIES ON THE ANTIRACHITIC ACTION OF HUMAN MILK. U. PELLEGRINI, Lattante **18**:65 (Feb.) 1947.

Growing rats, weighing approximately 65 Gm., were fed rickets-producing diets. When 3.5 to 7 cc. of human milk was added to the diet, rickets still developed in the animals. However, those receiving the human milk were livelier and gained more weight than the control animals. The more human milk taken, the better was the condition of the animals. Rats receiving fresh human milk did better than those given milk expressed from the breast twelve hours previously.

HIGGINS, Boston.

VITAMIN D INTOXICATION: REPORT OF A CASE. MARIT SKATVEDT, Ann. pædiat. **168**:148 (March) 1947.

The patient was a girl 1 year of age who, during approximately six months, had been given 6,500,000 international units of vitamin D. She was in a depressed state of health, with loss of weight and vomiting spells. The blood calcium level was remarkably high, up to 19.8 mg. per hundred cubic centimeters, which is almost twice the normal value. The nonprotein nitrogen content of the blood was increased. An almost isosthenuric condition was noted. Roentgenograms revealed a hypercalcified zone in the metaphysis, but no calcifications were visible in the arteries. The electrocardiogram showed changes, mostly in the T waves. After regulation for two and one-half months, most of the pathologic signs had disappeared.

Few reports of vitamin D intoxication have been published in Scandinavia. However, usually only cod liver oil was used earlier for children, as well as for adults. In the previously reported cases, all of which ended in death, only 1 child had received cod liver oil; the others had been given concentrated vitamin D

preparations. Three of the 5 children who died had hyperpyrexia and uremia. The kidney seems to be the organ that suffers first. First of all, cylinders of calcium seem to form in the lumen of the tubules. The only treatment the author's patient received was the maintenance of an acid urine with ammonium chloride until the blood calcium level was normal. He reasoned that the calcium phosphate is more easily dissolved in alkaline urine, and it is in the period that the blood calcium decreases that the risk of metastatic calcifications of fatal nature is greatest, according to Ham and Portuendo.

To avoid overdosing of vitamin D in the future, it is perhaps safest to warn against treatment with massive doses in usual practice, and perhaps to keep the highly concentrated vitamin D preparations in specially marked bottles.

FROM THE AUTHOR'S SUMMARY.

Newborn

THE MOST UNPHYSIOLOGICAL PERIOD OF LIFE. EDWARD B. SHAW, California Med. **66**:1 (Jan.) 1947.

During the last few years, because most infants have been delivered in hospitals, they have been subjected to artificial conditions which depart from the physiologic norm.

Anoxia produced by hypnotic, narcotic and anesthetic drugs used to alleviate labor pains and expedite delivery may have far reaching and dismal effects on the nervous system of the infant.

The introduction of a solution of silver nitrate into the tearless eyes of the infant produces chemical conjunctivitis, obstruction of the nasolacrimal duct and sometimes interference with early ocular fusion as an end result.

Physicians and nurses seem to do everything possible to thwart maternal nursing. Enforced separation of mother and child interferes both with normal feeding and with the establishment of an adaptation between them. The baby kept in a hospital nursery runs an increased risk of infection of the skin, the gastrointestinal tract and the respiratory system. Circumcision of baby boys has become almost routine.

Dr. Shaw urges that attempts be made to modify the care of the newborn infant in the following direction: 1. Mothers should receive a minimum of medication as a preliminary to delivery compatible with relative freedom from severe pain. 2. Chemotherapeutic and antibiotic substitutes for Credé's prophylaxis should promptly be discovered and introduced. 3. Maternal nursing should be reaccepted as the normal method of feeding and honest efforts made to encourage it, not to defeat it. 4. Added opportunity should be provided for mother and infant to effect an acquaintance and adaptation during the lying-in period. 5. Circumcision should not be proposed as a medical necessity unless better justification for it can be advanced than has been. PRYOR, Redwood City, Calif.

THE PREVENTION OF RH ISOIMMUNIZATION DUE TO BLOOD TRANSFUSION. J. W. DAVENPORT JR., New Orleans M. & S. J. **99**:376 (Feb.) 1947.

Tests for demonstrating Rh isoimmunization have increased both in number and in accuracy. There is still no way known permanently to inhibit or neutralize the antibodies once formed.

The Rh complex is highly antigenic. Some Rh-negative persons may become sensitized or isoimmunized by the entrance of Rh-positive blood through transfusions or pregnancy or both. One injection of Rh-positive blood to an Rh-negative person rarely sensitizes. Only 15 per cent of the white race are

Rh negative, and of these only 5 to 50 per cent become sensitized, even after several exposures. There is no method of determining which Rh-negative persons may be capable of being sensitized.

Prevention of sensitization is, therefore, important. The repeated transfusion of the Rh-positive blood into Rh-negative recipients very infrequently produces isoimmunization. At times it does occur in both sexes but produces a lesser degree of antibody formation than do Rh-positive fetuses in Rh-negative mothers. Practically the only weapon there is at present for preventing isoimmunization is the routine typing of all patients who are to be given transfusions and the giving to Rh-negative patients only Rh-negative blood. This procedure is especially important for women of child-bearing age or younger. Intramuscular injection of blood has the same effect as a transfusion.

Ideal situations are difficult to achieve because of the scarcity of reliable Rh-testing serums and Rh-negative donor blood.

Three illustrative cases are presented, with a discussion of the problems involved.

BERKLEY, Beverly Hills, Calif.

Acute Contagious Diseases

DIPHTHERITIC HEART DISEASE. MISCHA J. LUSTOK, Wisconsin M. J. **46**:215 (Feb.) 1947.

This report is a qualitative study of cardiac complications of diphtheria observed in a base sector of the European Theater during the spring 1945. The true incidence of such complications can be known only through electrocardiographic studies but may be assumed to be about 20 per cent. The strain of the organism was probably different from that common in the United States. There was no demonstrable relationship between intensive use of antitoxin or severity of infection and the development of cardiac complications. The pathologic changes were entirely myocardial, with degeneration, cellular infiltration and necrosis. Clinical diagnoses could be made only after cardiac involvement was fairly well advanced. Electrocardiographic patterns were of two types: Those of group 1, carrying a better prognosis, consisted of inversion of T waves and depression of S-T segments, especially in leads 1 and 2. The group 2 pattern, carrying a worse prognosis, showed auriculoventricular disassociation and conduction defects. A superimposed pattern of left ventricular strain was observed in severe cases. Treatment consists of effective management and prophylaxis of diphtheria infections. Reevaluation of the effectiveness of stock biologic preparation is suggested. Active treatment is nonspecific and supportive. Rest in bed until electrocardiographic changes have regressed or become stabilized is important. There is good evidence that patients who have no complications during the clinical course of the disease will have no late manifestations. The future course of patients recovering from diphtheria with myocarditis is not known.

BAIRD, Wauwatosa, Wis.

POSTDIPHTHERITIC POLYNEURITIS WITH PARALYSIS: REPORT OF A CASE. FERNANDO LÓPEZ CLARES, Bol. méd. d. Hosp. inf., México **1**:27 (July-Aug.) 1944.

A 5 year old girl was admitted to the hospital complaining of difficulty in swallowing liquids, which were coughed up and expelled through the nose. At the same time, there was a reeling gait and a temperature of 38.5 C. (101.3 F.).

The child had had measles one month previously, and soon afterwrd contracted diphtheria. Diphtheria antitoxin, 18,000 units, was given in small doses over four days.

In the ward, a paralysis of the soft palate, a nasal voice, paralysis of the lower limbs and other neurologic symptoms were observed, which, together with the laboratory findings, confirmed the diagnosis.

Treatment was with sulfadiazine, a vitamin B_1 preparation, strychnine, sulfate and neostigmine. The patient was discharged one and a half months later completely cured.

MADERO, México, D. F., Mexico.

DIPHTHERIA AND POLIOMYELITIS. A. CURBELO, A. CLERCH Y RIUS, E. MARRERO VELA and C. VEGA AGUILAR, Rev. cubana pediat. **18**:621 (Oct.) 1946.

The authors discuss the report of high incidence of positive reactions to the Schick test in children who had poliomyelitis. They investigated 40 children with poliomyelitis as to the result of preceding bacteriologic studies on the nasopharynx. None of the children had had diphtheria or immunization against diphtheria. Fifty per cent of the children had negative reactions to the Schick test, which means that the resistance against poliomyelitis and the resistance against diphtheria are different phenomena. No Corynebacterium diphtheriae (Klebs-Löffler) but a large number of other corynebacteria was observed, especially Corynebacterium xerose.

KEITH, Rochester, Minn.

Acute Infectious Diseases

TOXIC AND IMMUNOLOGICAL PROPERTIES OF PNEUMOCOCCAL HEMOLYSIN. SEYMOUR P. HALBERT, BARNETT COHEN and MARIE E. PERKINS, Bull. Johns Hopkins Hosp. **78**:340 (June) 1946.

Concentrates containing hemolytically active (reduced) pneumococcic hemolysin were shown to possess lethal and dermotoxic properties. The reversibly oxidized hemolysin was nonhemolytic and nonlethal and produced somewhat delayed dermonecrosis. Brief exposure of the concentrates to heat at 60 C. (140 F.), or to cholesterol, abolished the hemolytic, lethal and dermal activities. Absorption with rabbit erythrocytes appeared to remove the hemolytic and dermotoxic qualities at approximately the same relative rates. Mice immunized with the concentrate were generally capable of withstanding a subsequent injection of at least twice the dose lethal for 50 per cent of the test animals. The dermotoxic activity was observed to be neutralized by specific antihemolysin serum.

The presence in the hemolysin concentrates of C carbohydrate, presumably in nonantigenic form for the rabbit, was indicated by the results of precipitin and precipitin-absorption tests.

The evidence indicates that the hemolysin has the properties of a toxin and strongly suggests that its hemolytic (in vitro), lethal and dermotoxic activities reside in one and the same protein component of the concentrates.

FROM THE AUTHORS' SUMMARY.

STREPTOMYCIN IN THE TREATMENT OF INFECTIONS: A REPORT OF ONE THOUSAND CASES. NATIONAL RESEARCH COUNCIL, THE COMMITTEE ON CHEMOTHERAPEUTICS AND OTHER AGENTS, J. A. M. A. **132**:4 (Sept. 7); 70 (Sept. 14) 1946.

The experimental data amassed in these articles cannot be abstracted. Special attention is called to the sections in the first article relating to preparation of streptomycin for injection and modes of administration and to those in the second article relating to dosage, toxicity and causes of failure.

BAIRD, Wauwatosa, Wis.

PARA-AMINOBENZOIC ACID TREATMENT OF ROCKY MOUNTAIN SPOTTED FEVER. LEWIS B. FLINN, JOHN W. HOWARD, CHARLES W. TODD and ELVYN G. SCOTT, J. A. M. A. **132**:911 (Dec. 14) 1946.

Para-aminobenzoic acid was found to be most effective in the treatment of 10 patients with Rocky Mountain spotted fever in Delaware.

Clinical studies suggest that the level of para-aminobenzoic acid in the blood is best kept in the optimum range of 30 to 60 mg. per hundred cubic centimeters by adjustment of dosage and fluid balance in each individual case.

FROM THE AUTHORS' CONCLUSION.

METABOLIC STUDIES IN LOUSE-BORNE TYPHUS: OBSERVATIONS ON SERUM ELECTROLYTE PATTERN, SERUM PROTEIN PARTITION, AND NITROGEN BALANCE. NICHOLAS A. TIERNEY and ANDREW YEOMANS, J. Clin. Investigation **25**:822 (Nov.) 1946.

Twenty-one unvaccinated Egyptian boys and men between the ages of 12 and 48 years were studied. The diagnosis of louse-borne typhus was confirmed by the Weil-Felix and the complement fixation tests.

Chloride balance studies showed that during the first two weeks of the disease serum chlorides were low, while urinary chlorides were absent or greatly decreased. On "salt-free" diets, serum chloride levels rose in 5 patients during the second or third week of illness. In 4 they remained unchanged, while in 2 patients they fell. Addition of salt (7 to 10 Gm.) to the diet caused the serum chlorides to rise higher and more abruptly. In 3 of these patients the rise in serum chlorides could not be accounted for by the difference in salt intake and output, because they continued to excrete most of the added salt. The authors explained this spontaneous rise in serum chloride by postulating a contraction in the extracellular space.

Carbon dioxide content, p_H and total protein measurements were normal in most patients. However, total base measurements gave normal values, thus giving an increase in undetermined acid anions (14 to 27 milliequivalents per liter) in all instances. Studies on the nature of this undetermined anion were not made, but in absence of azotemia retention of inorganic ions $HPO_4^=$ and $SO_4^=$ was considered unlikely.

Despite normal serum proteins, the majority showed depression of the albumin fraction and striking elevation of globulin fraction. The latter fraction increased by 40 per cent after the third week of disease and in the face of declining Weil-Felix titers.

There was no relation between nitrogen output and intake or between protein destruction and azotemia. The patients on low protein diets consistently showed large nitrogen deficits and loss of weight. Those receiving high protein diets in the acute phase showed decidedly diminished nitrogen deficits and less loss of weight. Five of these patients actually had positive nitrogen balances during both the acute and the convalescent phases. The type of diet did not affect the amount of protein lost or the serum protein levels. However, the patients on high protein diets did have shorter convalescent periods and appeared stronger and better nourished than the others.

BRODSKY, Cincinnati.

IMMUNIZATION WITH TETANUS TOXOID. ANGUS MCBRYDE AND MARY A. POSTON, J. Pediat. **28**:692 (June) 1946.

The striking increase in the antitoxin content of the serum resulting from the subcutaneous injection of 0.004 cc. of tetanus toxoid U. S. P. five years after the original immunization would lead one to believe that the stimulating

dose may be unnecessary, although caution dictates its use. When the basic immunity has been well established, the presence of actual infection should cause the immunized person to respond with rapid formation of antitoxin. The response in our series was rapid and adequate, regardless of the level to which the antitoxin had fallen in the period since primary immunization.

This series was composed entirely of Negro children. It has been stated occasionally that the Negro child reacts with greater formation of antitoxin than does the white child. If this is true, it may explain the higher antitoxin levels obtained by us than those of other workers. The ages at the time of the primary immunization varied from 3 to 8 years. The children were almost equally divided as to sex. No difference in response to antitoxin was noted for either age or sex. The interval of two and one-half months between the primary doses resulted in an adequate response. Bigler and Werner reported that the optimum interval between injections was three months. Reactions were not severe in any of the children. All those of school age were able to continue in school. About 10 per cent of the children complained of soreness at the site of injection. Twenty-four hours after the intracutaneous injection of 0.1 cc. of tetanus toxoid, alum precipitated U. S. P., an area of erythema, varying from 2 to 6 cm., was noted. A small nodule was formed, which disappeared in about four weeks. No abscess formation or necrosis occurred.

One would expect severe cutaneous reactions in white children, so that plain tetanus toxoid probably would be better as a routine intradermal stimulating substance.

FROM THE AUTHORS' ABSTRACT.

TAKATA AND UCKO REACTIONS IN VISCERAL LEISHMANIASIS. ARRIGO DE LUCA, Pediatria **54**:397, 1946.

The author studied the behavior of reactions to the tests of Takata and Ucko for hepatic function in 13 children with leishmaniasis.

Positive reactions (9 cases of 13) are ascribed to disturbance in serum colloids due to the increased amount of euglobulin, which was caused by the involvement of the reticuloendothelial system by the leishmaniasis.

FROM THE AUTHOR'S SUMMARY.

HEMORRHAGIC DIATHESIS IN INFANTILE LEISHMANIASIS. GIACOMO PARRINELLO, Pediatria **54**:432, 1946.

The author made tests for hemorrhagic diathesis in 21 children with visceral leishmaniasis and obtained the following results: constant reduction in blood platelets, remarkably increased bleeding time, slightly increased coagulation time and retarded clot retraction, especially at the beginning of the test. The reactions to the Matas, Hammer, pinch, Hess and Koch tests were constantly negative. The blood pressure in 12 children was consistently low. The author expressed the belief that many factors may have part in the production of these changes, such as anatomic alterations in the blood vessels and changes in the bone marrow or spleen and metabolic rate, all of which influence the vegetative nervous system.

FROM THE AUTHOR'S SUMMARY.

ONCHOCERCIASIS IN A YOUNG CARDIOPATHIC PATIENT. ANTONIO PRADO VÉRTIZ, Bol. méd. d. Hosp. inf., México **1**:41 (July-Aug.) 1944.

A 13 year old boy, a native of Tapachula, Chiapas, was admitted to the hospital with complaints which led to the diagnosis of rheumatic carditis, onchocerciasis, pellagra and cutaneous papulonecrotic tuberculosis. These diagnoses were verified by means of laboratory studies and roentgenograms.

The patient had a small cyst in the right scapular region. This cyst contained Onchocerca volvulus and microfilariae. The author, in the last part of his article, discusses the treatment used. The head of the laboratory describes the technics employed for the identification of the filariae. MADERO, México, D. F., Mexico.

AMBULATORY TREATMENT OF INFANTILE GONORRHEA WITH PENICILLIN BY MOUTH. A. WIEDERHOLD and A. MENDEZ, Rev. chilena de pediat. **17**:367 (June) 1946.

Encouraging early and late results are reported for patients with gonorrhea between the ages of 8 months and 13 years, 8 of whom had not been treated previously. Therapy consisted of 100,000 units of penicillin sodium in 15 cc. of isotonic sodium chloride solution, divided into three daily doses of 5 cc. each, with the addition of a 4 per cent solution of sodium citrate and saccharin. Some of the factors leading to relapse are described. Twenty-five determinations of penicillin levels in blood and urine were carried out at one-quarter, one-half, two, three and four hours; no penicillin was recovered after three hours.

PLATOU, New Orleans.

Chronic Infectious Diseases

THE CONCENTRATION OF PENICILLIN IN THE SPINAL FLUID FOLLOWING INTRAMUSCULAR ADMINISTRATION IN NEUROSYPHILIS. LAWRENCE I. KAPLAN, HILTON S. READ, FREDERICK T. BECKER and CHARLES F. SEYMOUR, J. Lab. & Clin. Med. **31**:317 (March) 1946.

Penicillin in doses of 30,000 units was administered intramuscularly to patients with neurosyphilis, and examination of the spinal fluid of these patients ten to one hundred and fifty minutes after injection did not reveal the presence of penicillin within the limits of the test employed (penicillin less than 0.125 unit per cubic centimeter). Since beneficial results often follow this form of treatment in cases of neurosyphilis, the authors suggest that the drug may penetrate the spinal fluid in therapeutically effective amounts, not detectable by the methods employed, or that penetration may be unnecessary because the disease is essentially vascular in nature.

WILKINSON, Galveston, Texas.

SARCOIDOSIS—A MANIFESTATION OF TUBERCULOSIS. CHARLES CAMERON and E. K. DAWSON, Edinburgh M. J. **53**:465 (Sept.) 1946.

Cameron, professor of tuberculosis at the University of Edinburgh, and Dawson, from the East Fortune Sanatorium and the research laboratory at the Royal College of Physicians at Edinburgh, discussed the etiology of sarcoidosis in an earlier paper, published in 1942. Since that time their conviction has grown that sarcoidosis is an atypical form of tuberculosis. They report the history and observations on a girl during childhood and later youth, whose case they followed until her death, in 1946. She had a rare combination of tuberculous and sarcoid changes.

The authors state that it is difficult to make a distinction between tuberculosis and sarcoidosis. Most of the differences in the two diseases are explainable if one accepts sarcoidosis as a noncaseating form of tuberculosis in a person who has high immunity but low sensitivity. Whether the disease is quiescent or becomes activated to the typical picture of tuberculosis rests on the maintenance or the loss of stable balance between host and parasite.

The authors discuss the pathologic changes in sarcoid lesions and reproduce excellent microscopic sections.

NEFF, Kansas City, Mo.

FRAGILITAS OSSIUM (LOBSTEIN'S DISEASE). F. MASSELOT and ARRIGHI, Presse méd. **53**:639 (Nov. 24) 1945.

A case is presented showing the typical deformities of fragilitas ossium, or Lobstein's syndrome (tibial deformities, like those of congenital syphilis; keel-shaped sternum, such as that seen in rickets, and ulcerative pyloric stenosis). The anterior curvature of the tibias was so great that they resembled boomerangs, and in the erect position the tibias nearly touched the insteps. The patient was a North African woman aged 50. Although the Wassermann reaction was negative, the etiologic factor was undoubtedly congenital syphilis.

DAFFINEE, Melrose, Mass.

FALSE, MISJUDGED AND FADED TUBERCULIN REACTIONS. ERIK TÖRNELL, Svenska läk.-tidning. **42**:1137 (May 4) 1945.

The author, who has great experience with tuberculin testing, criticizes the examinations made by those who maintain that a positive tuberculin reaction frequently becomes negative after a certain time. Usually the reactions that disappear are those which are only slightly positive with a large dose of tuberculin and which are probably misjudged. Sometimes a traumatic reaction by scratching with the fingers of the children may produce a false positive tuberculin reaction. The author himself has seen only rare instances of faded tuberculin reactions and is of the opinion that the number of such cases is less than 0.1 per cent of the positive reactions yearly.

WALLGREN, Stockholm, Sweden.

Diseases of Blood, Heart and Blood Vessels and Spleen

HEART CATHETERIZATION IN INVESTIGATION OF CONGENITAL HEART DISEASE. ARNOLD L. JOHNSON, DELBERT G. WALLIN and JANICE B. ROSS, Canad. M. A. J. **56**:249 (March) 1947.

The present report is based on the study of 17 children with congenital heart disease. The age of the patients ranged from 19 months to 16 years. Four were cyanotic, and the rest were acyanotic. All four chambers of the heart were entered, as well as the pulmonary artery and its branches and the pulmonary veins.

The procedure employed, which is described in detail, was similar to that described by Courmand and Ranges. A number of roentgenograms are shown, and detailed discussions of several of the cases are included.

The conclusion is that the method of cardiac catheterization appears to be a useful adjunct in the investigation of congenital heart disease.

MOORE, Omaha.

THE RH FACTOR. RENATA DE BENEDETTI, Arch. ital. di pediat. e puericolt. **11**:146 (March) 1946.

By way of introduction, the author examines the principal studies of Landsteiner and his collaborators on animals, particularly those on anthropoid and inferior monkeys. These investigations have enabled the individualization of groups, subgroups and properties of human blood according to the serum reaction with the blood of these animals. She refers to studies on the property recently discovered—the relation of human blood groups and those of inferior monkeys, particularly of Macacus rhesus—the Rh factor.

The author describes the technical methods used in obtaining blood and carrying out serum tests, as well as the methods of comparison. She discusses the hereditary transmission of the Rh factor, emphasizing its importance in genetics, in anthropol-

ogy, in legal medicine and, above all, in clinical practice (transfusions) in cases of obstetric and neonatal pathologic conditions (erythroblastosis fetalis).

The author considers finally the diagnostic and therapeutic methods suggested in the recent American literature.

FROM THE AUTHOR'S ABSTRACT.

PURULENT PERICARDITIS TREATED WITH PENICILLIN: OBSERVATIONS ON A TWO MONTH OLD GIRL. J. P. GARRAHAN, G. F. THOMAS and J. A. CAPRILLE, Arch. argent. de pediat. **25**:419 (June) 1946.

A summary of the clinical history of a 2 month old girl is given. A puncture of the pericardial sac through the epicardium was made; 30 cc. of purulent material, containing numerous staphylococci and a few streptococci, was obtained. Ten thousand units of penicillin was given intramuscularly every four hours. Four more punctures in the pericardial sac were made; the first two punctures were followed by the injection of 6,000 units of penicillin in 6 cc. of isotonic sodium chloride solution U. S. P. Three weeks after the infant's admission to the lactating infants' service, the abdomen was observed to be distended, and a week later 300 cc. of ascitic fluid was aspirated. The baby lost ground progressively and died.

Cyanotic softening of the cardiac sounds and enlargement of the liver are pointed out as useful signs in the diagnosis of pericarditis. Observation of these symptoms must be supplemented by roentgenologic and electrocardiographic studies.

ROJAS, Boston.

INFANTILE HYPERTROPHY OF THE HEART. JÜRG SCHNEIDER, Helvet. pædiat. acta **1**:368 (July) 1946.

A boy 9 months of age died unexpectedly of cardiac insufficiency accompanied with increased pulse rate and a somnolent condition. Postmortem examination revealed severe hypertrophy of the heart with increased storage of glycogen. The case was considered one of the cardiac type of glycogenosis. The islands of Langerhans in the pancreas were increased. Definite storage of glycogen was observed in the central nervous system, as well as modification of the neuroglia and ganglion cells and isolated cellular inclusions. The possibility of a disturbance of central origin as a cause of glycogenosis is referred to.

FROM THE AUTHOR'S SUMMARY.

Diseases of Nose, Throat and Ear

THE TREATMENT OF MASTOIDITIS IN CHILDREN. L. H. LEESON, Canad. M. A. J. **56**:298 (March) 1947.

Leeson concludes that while the sulfonamide drugs, penicillin and streptomycin have definitely decreased the number of cases of acute mastoiditis, there are still a number of patients who must be operated on. Besides frank mastoiditis, masked mastoiditis is discussed.

Patterson and Smith analyzed 120 consecutive cases of this type and divided them into the following groups: (1) Cases evidenced by diarrhea and vomiting 49. Pus was found in the mastoid process in 35. (2) Cases with unusual conditions of the respiratory tract. Of the 30 cases in this group pus was present in 17. (3) Cases with marasmus. In 6 of the 12 cases pus was found in the mastoid process.

The bacteria were not of any characteristic group. Details of medical and surgical care are given.

MOORE, Omaha.

A Study of Voice Change in Boys Between the Ages of Eleven and Sixteen. Charles P. Pedrey, Speech Monogr. **12**:30, 1945.

A check was made on 1,014 boys between 11 and 16 years of age with respect to change of voice together with information on weight, height and pubic development. Chronologic age is the most consistent factor in determining onset of change of voice. The great shift in the direction of the adult voice occurred, on the average, at the age of 14, although 1.29 per cent of boys had adult voices at the age of 11. Of prepubescent boys, 23 per cent still had childish voices, while in 75.5 per cent the voice was beginning to change. At the pubescent level, 89 per cent of the boys were in process of change of voice. Age and amount of pubic development were equally reliable as indexes of the stage of voice development, the correlations being 0.65 and 0.68, respectively. Voice break may occur at any age. Approximately half the boys studied recalled having the voice break, half of whom, in turn, reported a feeling of embarrassment because of the break.

Palmer, Wichita, Kan.

Pathologic Deviations in the Child. Sergio Levi, Riv. clin. pediat. **45**:161 (March) 1947.

The author, after examining the physiology and normal evolution of speech, background necessary for an exact interpretation of pathologic deviations, discusses the alterations in speech in children and their therapeutic treatment, especially in regard to functional reeducation.

Various clinical cases, which had included orthophonic and logopedic treatment, are cited as examples. From the Author's Abstract.

Congenital Laryngeal Stridor Caused by Double Aortic Arch. D. Benesova, K. Vlasak and Frantisek Zuleger, Pediat. listy **1**:54, 1946.

This paper is divided into two parts: the clinical and the pathologic aspects. In the first part, 2 cases of severe congenital stridor due to an anomaly of the blood vessels are reported. Both ended fatally. In the pathologic portion, the authors try to explain the development of this anomaly on embryologic grounds. The actual cause of the stridor in both cases was a double aortic arch which, like a ring, compressed the trachea and the pharynx.

From the Authors' Summary.

Diseases of Lungs, Pleura and Mediastinum

Observations on the Volume of the Pulmonary Circulation and Its Importance in the Production of Cyanosis and Polycythemia. H. B. Taussig and A. Blalock, Am. Heart J. **33**:413 (April) 1947.

Diminished blood flow to the lungs, such as occurs in the tetralogy of Fallot, causes unsaturation of the arterial blood. When this is extreme and persistent, the condition leads to the development of polycythemia.

In patients in whom cyanosis and polycythemia result from lack of adequate circulation to the lungs, increasing the circulation to the lungs increases the oxygen saturation of the arterial blood, lessens the cyanosis and leads to a reduction in the polycythemia.

An oxygen saturation of 75 to 88 per cent can usually be attained in patients with tetralogy of Fallot by an anastomosis of the proximal end of the innominate artery to the side of one of the pulmonary arteries. At such a level of oxygen

saturation in the arterial blood, the stimulus for the production of polycythemia has been withdrawn.

An oxygen saturation of 65 to 70 per cent may be sufficient to enable the child to indulge in unrestricted activity and does not necessarily lead to the development of polycythemia.

FROM THE AUTHORS' SUMMARY.

ETHYL-NOR-EPINEPHRINE BY INHALATION FOR BRONCHIAL ASTHMA: A COMPARISON WITH EPINEPHRINE. MILTON M. HARTMAN, J. Allergy **17**:106 (March) 1946.

The effect of 2 per cent ethyl-nor-epinephrine (1-[3,4-dihydroxyphenyl]-2-amino-1-butanol) solution is compared with that of 1 per cent epinephrine solution in bronchial asthma. The bronchodilator effect of the drugs in uncomplicated asthma is about equal. In asthma complicated by infection, epinephrine is more effective.

Undesirable local effects on the upper respiratory tract do not occur with ethyl-nor-epinephrine. Toxic effects from inhalation of the drug occur less frequently and are not so serious as those from inhalation of epinephrine.

HOYER, Cincinnati.

VOLUNTARY BREATHHOLDING: I. PULMONARY GAS EXCHANGE DURING BREATHHOLDING. CHARLES D. STEVENS, EUGENE B. FERRIS, JOSEPH P. WEBB, GEORGE L. ENGEL and MYRTLE LOGAN, J. Clin. Investigation **25**:723 (Sept.) 1946.

Sixty underwater weighing experiments were performed on subjects during periods of voluntary breathholding. During breathholding there was a consistent, steady gain in weight, ranging from 200 to 500 Gm. per minute, in each subject. The rate of gain in weight was greatest in those subjects who had previously inhaled 100 per cent oxygen, as compared with the rates in those who had first inhaled 10 per cent oxygen or room air. The authors interpreted this decrease in buoyancy as due to a diminution of gas volume in the lungs.

Vital capacities (maximum expiratory volumes) were determined for the subjects after breathholding. Data were presented which showed a decrease in the vital capacity as the breath was held, and the rate of change was of the same order of magnitude as that occurring under water.

The rate of change in the gas volume of the lung under water was shown to be significantly slower than the rate of oxygen uptake as measured with a Benedict-Roth metabolism apparatus. The authors assumed the difference was due to small accumulations of gaseous carbon dioxide in the lungs during breathholding. Urinary loss of carbon dioxide was calculated during breathholding and was demonstrated to account for less than 1 per cent of total production of carbon dioxide.

Most of the carbon dioxide was retained by solution in the blood and tissue fluids during breathholding, as shown by an increase in arterial carbon dioxide tension amounting to a little more than 0.5 per cent by volume per minute. Arterial oxygen content dropped during breathholding after inhalation of room air and of ambient air at 16,000 feet (4,877 meters), but showed no significant drop after inhalation of 100 per cent oxygen.

The authors concluded that the decrease in lung volume occurred because oxygen diffused out of the lungs much faster than carbon dioxide diffused into them. The rate of change of lung volume was directly related to the oxygen tension of the initially inspired air. After inhalation of 100 per cent oxygen, the rate of change in lung volume was only slightly less than the oxygen consumption of the body.

BRODSKY, Cincinnati.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

ACUTE HEPATITIS IN CHILDREN. C. H. WEBB, S. GEORGE WOLFE, R. T. LUCAS and C. E. ANDERSON JR., South. M. J. **40**:340 (April) 1947.

The authors centered their discussion about a group of 43 cases of acute hepatitis observed in Louisiana. One half of the cases were nonicteric. Considerable stress was laid on the demonstration of bile in the urine (by the modified methylene blue test) and the finding of abnormal lymphocytes in the blood. These lymphocytes were similar to but not identical with those seen in the blood of patients having infectious mononucleosis. In this series of cases the disease was rather mild. The authors advocated a diet high in protein, low in fat and adequate in carbohydrate and vitamins.

LOGAN, Rochester, Minn.

CONGENITAL OCCLUSION OF THE BILE DUCTS. G. MAGGIONI, Arch. ital. di pediat. e puericolt. **11**:228, 1946.

The author describes 6 cases of congenital occlusion of the bile ducts, with chronic jaundice, acholic feces, urinary bile pigment and hepatosplenomegaly, in children from 3 to 5 months of age (3 boys and 3 girls). Two children were operated on without success; 3 were examined post mortem (in 1 child the stenosis appeared to be incomplete).

The author discusses briefly the various opinions concerning pathogenesis and concludes that, instead of adopting a single explanatory hypothesis for all cases, it seems much better to admit the possibility of various pathogenic elements, although the persistence of an embryonic occlusion is the most usual one.

Among the clinical signs, hemorrhage is stressed as a frequent cause of death. Of the cases observed by the author, 5 presented more or less considerable hemorrhagic manifestations (2 patients died in consequence of profuse melena). In 4 cases hypoprothrombinemia was noticed. In 2 of these cases it was hardly possible to improve the condition; in the other 2 cases a good effect was obtained by injections of vitamin K. This situation is ascribed by the author to the varying degrees of hepatic injury. The eventual hemorrhage may be due to hypovitaminosis K in those cases which answer readily to vitamin therapy.

The examination of the blood demonstrated normochromic or hypochromic anemia, with slight eosinophilia in the leukocyte formula; constantly increasing bilirubinemia (up to 24 mg. per hundred cubic centimeters). The direct van den Bergh reaction was positive for obstructive jaundice in all cases except 1; the indirect reaction was always positive.

The roentgenologic study, made with contrast mediums given by mouth (in 2 cases) or by intravenous injection (1 case), demonstrated neither the gallbladder nor the bile ducts.

The research on the alimentary fat exchange in 1 case (a child nourished exclusively with mother's milk) showed a good absorption (67 per cent to 78 per cent of the total ingested amount) with good digestion as well. In this case also, calcium levels in the blood were normal, while values for phosphorus were low.

Of the 2 cases in which operation was performed, 1 presented anatomic possibilities of success. Postmortem examination showed considerable hypoplasia of the bile ducts, incomplete occlusion of the choledochus and a normal gallbladder. In 2 other cases, complete atresia of the choledochus, conspicuous hypoplasia of the bile ducts and rudimentary gallbladders were seen. The histologic examination of the liver in these cases demonstrated a cholestatic biliary scirrhus in various degrees of evolution.

The author stresses the importance of early diagnosis and surgical treatment, because these patients may be saved only through formation of an artificial communication between the liver and the intestine.

FROM THE AUTHOR'S SUMMARY.

TREATMENT OF PYLOROSPASM AND PYLORIC STENOSIS BY SHORT WAVE RADIATION. G. BROGI, Lattante **18**:1 (Jan.) 1947.

Relief of pylorospasm occurred in 14 infants following the application of short wave irradiation therapy. The wavelength used was 6 meters, with electrodes applied over the epigastrium and to the back. Treatment was daily or every other day, with ten applications in all of ten to fourteen minutes each.

HIGGINS, Boston.

TREATMENT OF INFANTILE DIARRHEA WITH CAROB FLOUR. E. SORAGNI, Lattante **18**:78 (Feb.) 1947.

The carob bean (the seed of the locust tree, *ceratonia siliqua)* is commonly used in Italy as a fodder for animals, and because of its sweetness it is eaten by children as a fruit. A flour has been prepared from the bean and marketed by an American manufacturer under the name of Arobon®. Analysis of the flour reveals 1 per cent fat, 4.5 per cent protein, 40 per cent soluble carbohydrates and 1.5 per cent pectin. A 5 per cent jelly is prepared for infants under 6 months of age, and a 10 per cent jelly for older children and adults, with boiling water and sweetened with saccharin. Infants are offered 150 to 200 cc. per kilogram of body weight daily.

Soragni found the preparations successful in the checking of infantile diarrhea of varying types. The nature of the carbohydrates and the pectin content may be the basis for the efficacy of the preparations.

HIGGINS, Boston.

FAMILIAL HEPATIC CIRRHOSIS AND OSTEOPOROSIS. ANNA SCHOO, Ann. paediat. **168**:271 (May) 1947.

Dr. Schoo describes a family with 3 daughters with cirrhosis of the liver and a disorder of the bones similar to rickets. She discusses the connection between hepatic diseases and osteoporosis and the possibility of treatment with vitamin D in some cases.

FROM THE AUTHOR'S ABSTRACT.

Diseases of the Genitourinary Tract

A STUDY OF AEROBIC STREPTOCOCCI ISOLATED FROM THE UTERUS AND VAGINA. K. EILEEN HITE and H. CLOSE HESSELTINE, J. Infect. Dis. **80**:105 (Jan.-Feb.) 1947.

A study of the physiologic characteristics of ninety-two strains of streptococci isolated from the vagina of patients with vaginitis and the uterus of normal and febrile puerperae is reported. The classification of these organisms and the significance of the findings are discussed.

The results of penicillin sensitivity tests indicate the resistance of some strains of streptococci from the female genital tract, a point likely to be of clinical significance.

TOOMEY, Cleveland.

CALCULI OF THE BLADDER DURING CHILDHOOD. J. GARRIDO LESTACHE Y CARERA, Acta pediat. españ. **4**:797 (June) 1946.

A complete discussion of the subject is presented, including symptoms, diagnosis, pathogenesis, pathologic modifications and medical and surgical treatment, with the presentation of 10 cases.

In children these calculi are more frequent than in adults, and they occur oftener in boys than in girls. The ages of the patients vary from 2 to 12 years. The commoner symptoms are pain during micturition, an unsteady stream of urine and diurnal incontinence. Hematuria is less frequent in the child than in the adult. Roentgenographic examination is the most useful method of diagnosis. As etiologic factors, the following may be considered: climate and geology, type of food and water, uric acid infarcts in the newborn, variations in the urine, the presence of foreign bodies and, finally, vitamin A deficiency. The treatment is surgical removal.

The calculi are frequently composed of a mixture of calcium salts and urates or pure urates, phosphates and oxalates or calcium carbonate.

KEITH, Rochester, Minn.

DOUBLE KIDNEY WITH ECTOPIC URETER OPENING INTO THE VESTIBULE OF THE VULVA. HERBERT STACPOOL, Bol. méd. d. Hosp. Inf., México **1**:47 (July-Aug.) 1944.

A 13 year old girl was admitted to the hospital complaining of involuntary and constant voiding of small quantities of urine. The physical examination revealed only abnormal moistness of the vulval vestibule, but, after careful observation, just under the urethral meatus a punctiform orifice was found from which discharged every five to six seconds a drop of a liquid resembling urine. Further specialized examinations and roentgenograms revealed the presence of a double kidney with an ectopic ureter on the left side. The treatment was surgical and the outcome uneventful.

MADERO, México, D. F., Mexico.

Diseases of the Ductless Glands; Endocrinology

FURTHER STUDIES ON EFFECTS OF WATER SOLUBLE VITAMINS IN EXPERIMENTAL DIABETES. O. H. GAEBLER and JAMES C. MATHIES, Endocrinology **39**:239 (Oct.) 1946.

Losses of weight and nitrogen and pronounced glycosuria occurred in several depancreatized dogs during deficiency of water-soluble vitamins, even though the food intake and the insulin dose remained constant and choline or other lipotropic factors were supplied. Control of diabetes was reestablished when thiamine, riboflavin, nicotinic acid, pyridoxine and pantothenic acid were added to the diet.

JACOBSEN, Buffalo.

PATHOGENESIS OF SO-CALLED THYMIC DEATH. MARCELLO BOLLETTI, Riv. di clin. pediat. **44**:729 (Dec.) 1946.

After a brief review of the clinical and anatomic aspects and the pathogenic theories of sudden death generally and of thymic death in particular, 4 cases of sudden death (3 with anatomic and histologic control) in children who had no anatomic signs of thymic hypertrophy are described.

The author concludes that all sudden deaths—*sine materia*—are of cardiac origin and produced by exaggerated vagal constitutional hypertonia and the term thymic death must be supplanted by the term vagal death.

FROM THE AUTHOR'S ABSTRACT.

DIABETES AND ITS TREATMENT; WITH REFERENCE TO A CHILD TREATED WITH 3:1 INSULIN. SALVADOR ZUBIRÁN and J. G. PAGOLA, Bol. méd. d. Hosp. inf., México **1**:1 (July-Aug.) 1944.

A 10 year old boy was admitted to the hospital with the diagnosis of diabetes. The treatment first instituted was with insulin and a special diet, but the

glycosuria was only partially controlled. In view of this, the diet was modified. The caloric intake was lowered by one third of the normal allowance. The amount of protein was increased, and a moderate quantity of carbohydrates was included, with reduction in fats. At the same time, 3:1 insulin was introduced.

It was observed that, with this regimen, the patient improved and gained weight. The sugar disappeared from the urine and the amount of sugar in the blood became normal.

In the last part of the article, the authors discuss the modern conception of diabetes and give general rules for the management of these patients and indications for the use of 3:1 insulin.

MADERO, México, D. F., Mexico.

DIABETIC NANISM. ORLANDO GARCÍA FAES, Rev. cubana pediat. **18**:465 (Aug.) 1946.

The author defines "nanism" as an entity characterized by small stature, with normal bone age, sexual development and mental development. He reports a case of "nanism," with hypogenitalism associated with diabetes mellitus and relates it to diverse endocrine disturbances, as well as to delayed treatment of the diabetes, with resultant undernutrition and its sequelae. Without making a certain or definitive diagnosis, he presents his case as one of "diabetic nanism."

KEITH, Rochester, Minn.

ENDOCRINOLOGY IN CHILDHOOD. JIRINA PISAROVICOVA-CIZKOVA, Pediat. listy **1**:161, 1946.

The most important points differentiating endocrinology in childhood and in adulthood are discussed. The growing organism, the greater activity of the endocrine glands, psychic and constitutional factors, variable reactions and repair of damaged tissues of the young organism are cited, as well as the difference in the range of normal values for laboratory studies, the great importance of prevention of diseases in childhood and clinical symptoms and signs peculiar to children.

FROM THE AUTHOR'S SUMMARY.

Diseases of the Muscles, Bones, Joints and Lymph Glands

TUBERCULOSIS AND ENDOCRINE DISTURBANCE IN A CHILD WITH MULTIPLE RHEUMATOID ARTHRITIS (STILL'S DISEASE). P. PROSPERI, Riv. di clin. pediat. **43**:101, 1945.

A case of chronic recurrent arthritis, accompanied with generalized external and internal adenopathy, fever and grave cachexia, in a child, 6 years old, is described. Macroscopic anatomic articular lesions were scarce, while nodular, caseous pulmonary tuberculosis, with miliary dissemination in the liver and spleen, and ulcerous tuberculosis of the first part of the small intestine were present. The histologic examination showed small parvicellular infiltrations about the vessels in the periarticular tissues, the aforementioned tuberculous lesions of the lungs, liver, spleen and lymph nodes, a slight scleroatrophy of the lymphadenoid tissue of the spleen and lymph nodes and signs of basophilia in the hypophysis, of hyperthyroidism and of hypofunction of the pancreatic islets.

The etiologic problem related to multiple rheumatoid arthritis (Still's disease), with special attention to its relation to tuberculosis and endocrine alterations, is discussed. The importance of the tuberculous infection as a pathogenic factor in the disease is emphasized, and it is suggested that the articular lesions might be the consequence of a special allergic state of the patient against the toxic action of the tuberculous infection. The disease might also be influenced by a dysfunction of the thyroid gland.

FROM THE AUTHOR'S SUMMARY.

OSTEOMYELITIS IN INFANCY. LHOTAK JAROSLAV, Pediat. listy **1**:58, 1946.

A series of 36 cases of osteomyelitis is divided into three groups. In the first group are cases in which the osteomyelitis developed simultaneously with the primary infection; in the second group, the primary infection subsided before osteomyelitis developed, but apart from the bony infection there was purulent infection of the adjacent joint and soft tissues. The third group includes only cases of pure infection of bone.

The prognosis for the first group depends, as far as mortality goes, on the primary infection. In the second group, life is not endangered but serious deformities of joints follow. In the third group, for which the prognosis is the most favorable of all, there are noticeable roentgenographic changes of the joint surfaces, even though the function of the joint is perfect, so that degenerative changes in the joint in later life may be expected. The clinical picture of osteomyelitis in relation to localization is discussed. The treatment in the first two groups is surgical, in the third conservative. In addition, penicillin, chemotherapy, transfusions and suitable diet are used.

FROM THE AUTHOR'S SUMMARY.

LIPOCHONDRODYSTROPHY (DYSOSTOSIS MULTIPLEX [PFAUNDLER-HURLER], GARGOYLISM). VLADIMIR KLUSKA and RICHARD ZEMANEK, Pediat. listy **1**:105, 1946.

A description of 2 cases is given, with detailed analysis of clinical symptoms and signs, roentgenographic findings and manifestations of the so-called phospholipid diathesis (DeRudder). A report of the histologic aspects of the disease is included (Kny and Schmidt). The authors state that it is unlikely that lipochondrodystrophy is a combination of dysostosis Morquio and the phospholipid diathesis (DeRudder), but they share the opinion of Ulrich that this disease, which is recessively hereditary, is transmitted by a single pathologic gene.

FROM THE AUTHORS' SUMMARY.

OSTEOMYELITIS IN CHILDHOOD. WILHELM SCHÄFFER, Wien. klin. Wchnschr. **58**: 697 (Nov. 22) 1946.

The author summarizes his experiences in the past year with 197 children with osteomyelitis. They ranged in age from infancy to 15 years. In this group 36 died, of whom 17 were under 1 year of age. Thirteen of the 36 died in the first week of illness. Schäffer recommends rest in bed, incision when there is abscess formation and later sequestrotomy. He warns against early incision into the bone. He states his opinion that blood transfusions in the early stage may lead to spread of the disease with the occurrence of metastatic abscesses. With these patients he abstained from transfusion until at least the second week of the disease. Schäffer lays little stress on the use of chemotherapeutic agents for these children and does not mention the use of antibiotic substances.

ABT, Chicago.

Skin Diseases; Allergy

TREATMENT OF CUTANEOUS HEMANGIOMA WITH RADIUM. EDUARDO CACERES, Am. J. Roentgenol. **56**:523 (Oct.) 1946.

The object of the treatment of hemangioma is the complete disappearance of the lesion without visible scar, atrophy or telangiectasis of the skin. The best results are obtained with small lesions. Radiosensitivity is greatest in early infancy, when the endothelial cells lining the blood spaces still retain their

embryonic character. The scar and pigmentation which occur in some cases diminish in time; hence, those lesions treated in infancy allow sufficient time to elapse for the scar to become inconspicuous before the patient becomes conscious of a physical defect. The optimum age for radium therapy is during the first six months of life. A rapidly growing hemangioma should be given immediate treatment. Ulceration is not a contraindication to radium therapy, but scarring will follow healing of the lesion.

The author discusses in detail the radium applicators, the selection of treatment and dosage. An analysis of 66 cases of hemangioma treated with radium is presented.

HARRISON, Chicago.

ALLERGY TO VIRUS AND RICKETTSIAL VACCINES: I. ALLERGY TO INFLUENZA A AND B VACCINE IN CHILDREN. BRET RATNER and SAMUEL UNTRACHT, J. A. M. A. **132**:899 (Dec. 14) 1946.

Of a group of 108 highly allergic children, 11 (10.2 per cent) showed a positive local reaction to the intradermal injection of 0.02 cc. undiluted influenza type A and B vaccine. One child had a systemic reaction (asthma) to the injection. One extremely sensitive child was tested only with the 1:10 dilution of the vaccine. All these children were sensitive to egg white protein. In only 5 of the children (5 per cent) were the reactions strong enough to make caution in the use of the vaccine necessary. One of these children had urticaria and asthma following the ordinary subcutaneous injection of 0.5 cc. of vaccine. Thus, about 5 per cent of allergic persons or 0.5 per cent of the total population may need special caution in administration of the vaccine. The authors suggest that the intradermal test precede all use of the vaccine, since its reaction is much more reliable than a history of allergy per se or even a history of allergy to egg. Attempts should be made to rid the vaccine material of egg protein.

BAIRD, Wauwatosa, Wis.

CONGENITAL MULTIPLE HEMOLYMPHANGIOENDOTHELIOMAS OF THE SKIN. G. MAINI, Lattante **18**:29 (Jan.) 1947.

A female infant displayed on the skin at birth many small red hemangiomas varying in size from the head of a pin to that of a small pea; otherwise, the child appeared normal. At the age of 40 days, the child was poorly nourished and wasting away. The tumors had grown to the size of nuts. One as large as an orange could be felt in the upper left quadrant of the abdomen. A biopsy specimen was taken, and the diagnosis of blastoma—hemolymphangioendothelioma—was made.

HIGGINS, Boston.

PROPHYLAXIS OF SERUM SICKNESS. GINO CARDINI, Riv. di clin. pediat. **44**:746 (Dec.) 1946.

The author describes the good results obtained in the prevention of serum sickness with the use of serum taken from patients convalescing from this illness. The sickness was prevented in 79.3 per cent of those treated. Only 3.4 per cent of the control group was immune.

The author, after examining the various theories on the pathogenesis of this illness, endeavors to interpret the results obtained through one of them, the immunobiologic theory.

FROM THE AUTHOR'S ABSTRACT.

ERYTHEMA NODOSUM IN TWO SIBLINGS. R. GARELLY DE LA CAMARA, Acta pediat. españ. **4**:781 (June) 1946.

This brief clinical note presents 2 cases of erythema nodosum in a 9 year old boy and his 12 year old sister. The onset was with fever, followed five to six days later by the appearance of a rash on the lower extremities. Tuberculin reactions were positive and roentgenographic changes were present in the chest. The etiology of erythema nodosum is briefly discussed.

KEITH, Rochester, Minn.

Miscellaneous

THE EFFECT OF SULFONAMIDES ON THE ACTION OF PENICILLIN. GLADYS L. HOBBY and MARTIN H. DAWSON, J. Bact. **51**:447 (April) 1946.

After the activity of penicillin against various micro-organisms had been discovered, it was observed that there was a conspicuous difference in susceptibility not only in organisms of different species, but in those within the same species. Therefore, it was suggested that in some circumstances the combination of other antibacterial agents with penicillin might be advisable when full bacteriostatic or bactericidal action was desired. The authors carried out experiments using sulfonamide compounds and penicillin. They concluded that the combination of penicillin and sulfadiazine produces at times a greater bacteriostatic effect in vitro than the same concentration of sulfadiazine or penicillin alone. However, specific experimental conditions are necessary to produce this effect, for details of which the original article should be consulted.

STOESSEN, Minneapolis.

THE INFANT OF THE OLDER PRIMIPARA. L. CUSMANO, Lattante **18**:89 (Feb.) 1947.

Cusmano gives statistics gathered from the records of the obstetric clinic in Parma, Italy. There were 374 infants of primiparas between 36 and 50 years of age. Of these infants 131 were premature, due to a shortened pregnancy. With 79 of these, the mother had had a toxemia of pregnancy, resulting in death in 27 of the infants. Only 11 of the other 52 premature infants died. There were 56 stillbirths and 38 neonatal deaths. Of the 280 living children, only 27 were not breast fed; 79 were only partially breast fed. Almost 50 per cent of the infants regained their weight at birth by the eighth day.

HIGGINS, Boston.

THE COMMONEST DIAGNOSTIC ERRORS IN DISEASES OF CHILDREN. P. O. LUNTZ, Pediatria, January 1945, Vol. 53.

In the author's experience the commonest serious diagnostic errors in pediatrics are made in the early stages of pneumonia, meningococcic meningitis and pharyngeal diphtheria.

Early lobar pneumonia with abdominal symptoms is frequently diagnosed as acute appendicitis, primarily because of inadequate clinical inspection and percussion. Light, comparative percussion of both sides of the chest, including the supraclavicular spaces, together with careful clinical inspection, will almost always enable the pediatrician to establish the correct diagnosis in the early stages of the disease, even before positive evidence is obtained by means of auscultation or roentgenogram.

Patients with meningococcic meningitis are frequently admitted to the hospital with diagnoses of central pneumonia, food poisoning, hemorrhagic diathesis and

even cerebral concussion. A careful inspection for the cutaneous manifestations in meningococcic meningitis may prevent such diagnostic errors in a large number of cases. The characteristics of these cutaneous manifestations, as well as the symptoms of early pharyngeal diphtheria, are described. The importance of early diagnosis is stressed. The author deplores the fact that the members of the younger generation of physicians usually rely more on laboratory aids for the diagnosis of these diseases than on their clinical acumen.

BODER, Los Angeles.

MORPHOLOGY OF PUS. VON ERICH NASSAU, Ann. paediat. **168**:277 (May) 1947.

The study of the morphology of pus makes possible the acquisition of details which may enable one to judge the degree of illness better and to make a more accurate prognosis. Such details may also provide suggestions regarding the necessary therapeutic measures.

FROM THE AUTHOR'S ABSTRACT.

OUR EXPERIENCE WITH PENICILLIN. JIRI BLECHA, KAMIL KUBAT and MILOSLAV TUTTER, Pediat. listy **1**:3, 1946.

Half a year after the institution of penicillin treatment, our results in 185 infants are as follows: The treatment proved to be extremely successful. The average dosage was 40,000 international units over a period of three to ten days. The usual treatment with sulfonamide drugs and transfusions was used as well. The largest number of cases was 112 of pyoderma in patients up to 3 months of age. In these children penicillin was the most effective treatment of all. The mortality rate in this group was still high (27.6 per cent), but it can be explained through the inclusion of moribund patients and those with complications who came to our hospital at the end of the war.

FROM THE AUTHORS' SUMMARY.

PREVENTIVE MEDICINE OF TODAY. A. RIPKOVA, Pediat. listy **1**:33, 1946.

It is proposed to centralize child welfare work and preventive medicine in the Ministry of Health, as child care is a specialized health problem.

FROM THE AUTHOR'S SUMMARY.

PATHOLOGIC CHANGES IN PUBERTY. A. MORES, Pediat. listy **1**:64, 1946.

A summarized survey of anomalies of puberty is given, to which disorders the medical profession must pay increased attention in the future.

FROM THE AUTHOR'S SUMMARY.

NECROSIS FOLLOWING INTRAMUSCULAR INJECTIONS OF SULFATHIAZOLE IN INFANTS. KAMIL KUBAT, Pediat. listy **1**:79, 1946.

Seven cases of necrosis following intramuscular injection of a sulfathiazole preparation (cibazol®) are reported and the intramuscular use of this drug in infancy is rejected.

FROM THE AUTHOR'S SUMMARY.

SO-CALLED INFANTILE LITTLE FINGER (DU BOIS'S SIGN). M. SCHACHTER, Helvet. pædiat. acta **2**:174 (April) 1947.

A comparative study of 200 problem children and 381 normal controls showed that the so-called infantile little finger, Du Bois's sign, is more frequent (27 per cent) among the latter than among the former (19 per cent). The greater frequency of the Carabelli tubercle and of the axiphoidia (aplasia of the xiphoid process) among the bearers of the infantile little finger is not sufficient to prove its heredosyphilitic nature. Control studies are still required.

FROM THE AUTHOR'S ABSTRACT.

News and Comment

GENERAL NEWS

International Congress on Rheumatic Diseases.—More than 150 physicians from foreign countries are expected at the International Congress on Rheumatic Diseases to be held at the Waldorf Astoria Hotel in New York city from May 30 to June 3, 1949. Many of these physicians will present papers before the plenary sessions which will be held in the mornings. In the afternoons clinics are scheduled at several of the New York hospitals.

Already many papers have been accepted for the congress. They include, in addition to presentations by prominent authorities in the United States, articles by numerous distinguished foreign guests. Among these are:

"Rheumatism, a National Problem," Lord Horder, London, England.
"The Treatment of Progressive Rheumatism with Copper Salts," Jacques Forestier, Aix-les-Bains, France
"Relations Between Rheumatic Fever and Rheumatoid Arthritis," Eric Jonsson, Stockholm, Sweden
"Transfusions of Blood from Pregnant Women in Patients with Rheumatoid Arthritis," Imre Barsi-Basch, Budapest, Hungary
"Procaine Infiltration in Painful Musculoskeletal Disorders," Prof. S. de Seze, Paris, France
"Statistical Analysis of 1000 Cases of Rheumatoid Arthritis in Relation to Insidious and Acute Onset, Menopause, Pregnancy, Psoriasis, Ankylosing Spondylitis and Still's Disease," Svend Clemmesen, Copenhagen, Denmark
"Some Aspects of Psychogenic Rheumatism," Dr. William Tegner, London, England
"Muscle Soreness and Myosis as a Symptom of Chronic Overstraining, Especially in Neurotic Persons," Henrik Seyfarth, Oslo, Norway
"Chronic Polyarthritis and Psoriasis," P. Barcelo, Barcelona, Spain
"Involvement of the Nervous System in Rheumatoid Arthritis," Veikko Laine, Heinolan, Finland
"Periarthritis of the Shoulder," Fernando H. Ramos, Montevideo, Uruguay

The official languages of the congress will be English, French and Spanish, but instantaneous translations of the scientific papers given at the plenary sessions will be made by means of the I.B.M. wireless system. The meeting is open, and the registration fee is $10.

Benjamin Knox Rachford Lectureship.—Dr. Joseph Stokes Jr., of Philadelphia, will deliver the seventeenth annual series of the Benjamin Knox Rachford Lectureships on Tuesday evening, Feb. 1, and on Wednesday evening, Feb. 2, 1949, at 8:30 p. m., in the auditorium of the Children's Hospital Clinic and Research Building, Cincinnati. The general title of his lectures will be "Viral Hepatitis."

Recipient of Award of Phi Delta Epsilon Graduate Club Announced.—The award of the Phi Delta Epsilon graduate club of Denver for 1948, in honor of Dr. Emanuel Friedman, professor of pediatrics, University of Colorado Medical School, was given to Mr. Louis Duman.

PERSONAL NEWS

Election of Dr. McIntosh Announced.—Dr. Rustin McIntosh, of New York city, has been elected chairman of the American Council on Rheumatic Fever.

Medical Head of Red Cross Blood Program Named.—Dr. Louis K. Diamond, of Boston, has been named Medical Director of the Red Cross National Blood Program.

Book Reviews

Epilepsy. Edited by W. G. Lennox, M.D., and others. Proceedings of the joint meeting of the Association for Research in Nervous and Mental Disease and the International League Against Epilepsy, Dec. 13 and 14, 1946. Price, $12. Pp. 654, with 167 illustrations. Baltimore: The Williams & Wilkins Company, 1948.

This book represents the proceedings of the joint meeting of the Association for Research in Nervous and Mental Disease and the International League Against Epilepsy, held Dec. 13 and 14, 1946, in New York city.

Among the papers included is a report on the study of 66 pairs of twins affected by seizures. The extreme ages of the twins were 6 months and 42 years. Two thirds were monozygotic; only one third of the twin births in the United States are monozygotic. Lennox reports recording the electroencephalograms of almost 500 near relatives of epileptic persons. He observed a much higher proportion of abnormal records in this group than would be noted in a random selection of the population. The data suggest that in the epileptic patient, patterns of electrical potentials, as well as patterns of clinical manifestations, may be genetic in origin. In uninjured monozygotic twins, the concordance of both the type of seizure and the type of dysrhythmia suggests that a transmitted predisposition exists not merely to seizures in general but to particular patterns of brain waves and clinical manifestations. An electroencephalogram made under standard routine conditions is not fully adequate. More intensive study with a larger series of patients, with utilization of the stimulating effects of sleep or drugs, may bring to the surface abnormalities that are at present submerged.

I. M. Scheinker in his paper presents the alterations in the cerebral white matter in epilepsy, with consideration of two types of lesions: (1) the vascular lesions observed in cases of epilepsy without history of trauma and (2) atrophic sclerosis of large areas of the white matter seen in cases of post-traumatic epilepsy. The diffuse sclerosis may be interpreted as sequela to prolonged circulatory disturbance following injury to the brain.

Another article concerns seizures in patients with brain tumors. The electroencephalographic changes are quite different from those in idiopathic epilepsy. Paroxysmal patterns are rare. Response to hyperventilation is even more rare. Seizures occurred in 34 per cent of the series of 506 persons with tumors of the cerebral hemispheres, including abscesses and subdural hematomas. Therefore, these patients have no predisposition to "epilepsy."

A subsequent report demonstrates that the convulsive activity of the brain is accompanied with an increase in its rate of glucose utilization. A technic is reported for estimating the minute volume flow of blood through the human brain.

In another study the reduction of seizure threshold observed in hydrated animals is correlated in part with the reduction in total electrolyte concentration and to a lesser extent with an apparent increase in the volume of intracellular fluid. The seizure threshold is reduced when body temperature is lowered and increased when body temperature is increased.

"Wheat Gluten As a Convulsant" concerns a study of electroencephalographic changes in 18 dogs in the rations for whom wheat gluten was substituted for

casein. The epileptic state is produced in dogs by the intake of wheat gluten. Typical electroencephalographic changes were recorded. These changes occurred as early as three days after the beginning of the gluten diet. The electroencephalographic abnormalities are comparable to those seen in human epilepsy.

During convulsive activity, as set forth in the next article, a new steady state of the cerebral metabolism is established, with a higher oxidative rate, a higher level of lactic acid and a lower level of phosphocreatinine than is characteristic of the cerebral metabolism during narcosis. The brain appears able to function at the higher level for an indefinite period of time in the presence of an adequate stimulus and an adequate oxygen supply.

The last paper in the section states that there is no reason for the belief that the increase in oxygen consumption is any other than a result of the increase in nerve activity. The maximum rate of consumption is reached only by the end of the convulsion, after which it gradually returns to the initial level, an observation which also agrees with the results of measurements of oxygen tension.

The next section of the book is devoted to electroencephalography.

The majority of epileptic patients have both petit and grand mal attacks and diagnosis by electroencephalography will be possible only if an attack is observed, when, in any case, clinical observation should be conclusive. Walter describes an automatic wave analyzer to perform a function similar to that of the Grass instrument but having the advantage of performing the analysis automatically in ten seconds every ten seconds and writing out the frequency histogram directly on the original primary record, with which it can immediately be compared. An attempt was made to precipitate seizures in patients known to have petit mal by reenforcement of the spontaneous rhythms. The easiest way to evoke rhythmic electrical activity in the brain at a selected frequency is by rhythmic photic stimulation flicker. This is convenient since the introduction of the high power electronic stroboscope which generates extremely intense flashes of light, each lasting only about 10 microseconds at any frequency desired.

Unfortunately, according to the second study in this section, the disorder in many patients has been diagnosed as idiopathic petit mal epilepsy on the basis of local, or even bilateral, synchronous epileptiform waves in the electroencephalogram which correspond roughly to the pattern of true petit mal. These patients were observed later to have symptomatic epilepsy due to brain tumor or some other form of local epileptogenic lesions of the brain. Practically all the detailed features of the electroencephalogram in petit mal epilepsy can be duplicated by rhythmic electrical stimulation of a local area in the anterior medial portion of the thalamus not greater than 2 square millimeters. All the features were reproduced experimentally in cats by rhythmic electrical stimulation with brief shocks to a small area.

A report is given on the significance of electroencephalographic findings in 202 of the children between the ages of 5 and 12 years who were admitted to the psychiatric ward in 58 "normal" siblings of 53 of these patients. Of the records of 161 children with behavior disorders, 104 were abnormal; 34 contained paroxysmal seizure patterns or spontaneous bursts of high voltage activity numbering 3 to 5 per second. Twenty per cent of these were in the group with behavior problems and 24 per cent in the schizophrenic children. Only 7 per cent of the records for controls had seizure patterns, while 46 per cent of those for the patients with organic involvement and 76 per cent of those for the epileptic children were so diagnosed. Of 102 records from normal children 4 to 11 years of age in the Children's Hospital, Boston, 85 produced a diagnosis

of normal; 10 were considered borderline and 7 grossly abnormal. Sixteen per cent of the total records were abnormal, a relatively high incidence for children who had only primary behavior disorders. The type of records differs from that of the child with epilepsy. The behavior disorder is characterized by dysrhythmia and spontaneous bursts of high voltage activity, but contains no spikes and has not the decided individual variability of the epileptic record.

One hundred and fifty-three children with febrile convulsions were studied clinically in another investigation. The boys outnumbered the girls 2 to 1. Heredity is important. Of the children 45 per cent had a family history of convulsions; 65 per cent had their first febrile convulsion between the ages of 1 and 3 years. It was unusual for a child to have only one febrile convulsive episode; severe convulsions occurred in a surprisingly high percentage (35). Fifty-two children were studied whose initial convulsion occurred with fever, but in whom recurrent convulsions or epilepsy have since developed. By contrast with the preceding group, the febrile convulsions which occurred in these children were severe in the majority (64 per cent). These clinical features may indicate an unfavorable prognosis. Electroencephalograms were obtained on all the children. Of the 153 children whose convulsions occurred only with fever, 55 per cent had a normal electroencephalogram. It is Margaret Lennox's personal opinion that the febrile convulsions are epilepsy, that the difference is one of degree rather than of kind.

Gibbs makes an excellent presentation of 500 children with epilepsy who were studied awake and asleep. He compares these results with those obtained on 90 normal control subjects. Patients with a history of epilepsy are more than twice as likely to show seizure discharges during sleep as during the waking state; seizure discharges are rare during sleep in normal persons. Studies during sleep more than double the clinical value of electroencephalography.

An electroencephalographic study of 212 cases of infantile cerebral spastic palsy shows the finding of seizure discharges in the absence of a history of seizures and suggests that clinically evident seizures may occur.

The first four chapters of the next section deal with reports on the hydantoin preparations. The next chapter is a report on the results of treatment with trimethadione (tridione®) and paradione® (3,5-dimethyl-5-ethyloxazolidine-2,4-dione). Lennox treated 245 patients with trimethadione. He reports that 85 per cent experienced improvement.

The following section begins with a report on 246 cases of penetrating wounds of the head studied in detail from all aspects.

The hyperventilation and hydration technics for precipitating seizures have not been successful, according to the second paper in this section. The use of metrazol (pentamethylenetetiazol) to produce convulsions has the distinct advantage that the attack may be produced at the time the patient is under observation. In a series of 97 post-traumatic cases of epilepsy, an attempt was made to activate the epileptogenic focus by hyperventilation, hydration, electric shock and the administration of alcohol, trimethadione, penicillin, acetylcholine, cyanide and metrazol® intravenously. Metrazol® proved to give the most satisfactory focal activation in approximately 44 per cent of the cases on the first test, and in a much higher percentage on repeated testing.

A study of minimal electroencephalographic response with metrazol® and other convulsant drugs is next presented.

In 39 cases of post-traumatic epilepsy, electroencephalograms were taken from the exposed cortex. In 14 cases spontaneous focal electrical alterations, such as isolated spikes, bursts of spikes or spiky waves, occurred from the cortex

adjacent to but not in the cerebral scar. Stimulation of cortical epileptogenic foci by low voltage electrical current induced an after-discharge lasting from a few minutes to as long as twenty-eight minutes.

A summary of the results of a study dealing with the incidence of "late epilepsy" among 279 cases of craniocerebral injury resulting from the war is given in the following chapter. Within the first two years following injury, seizures developed in 36.2 per cent; of these, according to the area of the brain injured, 26.7 per cent were frontal injuries; 50.7 per cent central; 33.3 per cent occipital, and 35.0 per cent, temporal.

In World War I, it is reported, 98.7 per cent of the epileptic persons discovered in the United States Army were considered to have had seizures prior to enlistment, while in World War II, 79.5 per cent of all epileptic persons found in the United States Navy were judged to have had this condition in some form prior to induction.

A report on 11 patients with epileptiform psychopathologic reactions who each had abnormal electroencephalograms is made. In 8 the abnormalities were nonspecific but not suggestive of epilepsy. Three patients had paroxysmal features suggestive of epilepsy.

The average private patient has better than average intelligence, states another report. Genetic or essential epilepsy is preferable to acquired or symptomatic epilepsy.

The intelligence quotient of a noninstitutional sample of the epileptic population is well within the normal limits according to the last study in this book. The epileptic groups and groups with personality problems are in such close agreement with each other that they seem to be two samples of the same population. Neither the group with epilepsy nor the group with personality problems was significantly different in intellectual characteristics from the norms for the general population.

Recent Advances in Obstetrics and Gynaecology. Seventh edition. By Aleck W. Bourne and Leslie H. W. Williams. Price, $6. Pp. 334, with 85 illustrations. Philadelphia: The Blakiston Company, 1948.

Like its predecessors, the current edition of "Recent Advances in Obstetrics and Gynaecology" is concise, authoritative and well written. It has been the authors' practice to select a few pertinent topics for review. Of these, the current edition contains several which are of particular interest to the pediatrician. The section dealing with lactation seems especially timely. The physiologic changes in the breast during pregnancy and lactation are considered in some detail. Failure of lactation is discussed, and several suggestions are made regarding its treatment. In the section on erythroblastosis, the stated purpose is to present the subject in the simplest possible manner. The authors assume at the outset that the reader's knowledge of this complex subject is something less than that of the expert serologist, and in a well ordered discussion they outline the features of Rh incompatibility which are considered useful to the practicing physician. To the initiated, this discussion may appear elementary. To those whose interests are chiefly in other fields, it will be most refreshing and informative.

Stillbirths and neonatal deaths are reviewed in some detail. The importance of respiratory and alimentary infection as a cause of neonatal death is discussed, and the protective value of globulin in the colostrum is emphasized. The principles of management of the premature infant are reviewed, and the prognosis for premature infants is discussed.

Other subjects considered include the anemias of pregnancy, use of anesthesic and analgesic agents in obstetric practice, cancer of the cervix, stress incontinence, roentgenologic diagnosis in obstetrics and gynecologic roentgen therapy. Throughout the book, much space is given to physiologic principles.

This volume is recommended not only to practicing pediatricians, obstetricians and gynecologists, but also to students interested in these subjects.

Teaching Psychotherapeutic Medicine: An Experimental Course for General Physicians Given by Walter Bauer, M.D., Douglas D. Bond, M.D., Henry W. Brosin, M.D., Donald W. Hasting, M.D., M. Ralph Kaufman, M.D., John M. Murray, M.D., Thomas A. C. Rennie, M.D., John Romano, M.D., and Harold G. Wolff, M.D. Edited by Helen Leland Witmer. Introductory chapter by Geddes Smith. Price, $3.75. Pp. 464, with no illustrations. New York: The Commonwealth Fund, Division of Publications, 1947.

This book represents a series of lectures on the various aspects of psychosomatic phases of the general practice of medicine given as postgraduate courses to physicians attending the University of Minnesota. A glance at the table of contents will convince the average physician of the practicability of the course. There are chapters on general orientation, the patient-physician relationship, normal personality development, psychotherapy, the meaning of a psychoneurosis, diagnosis of psychoneurosis, anxiety, general principles of psychotherapy, special therapies, common psychopathology, care of veterans, life situation, emotions and disease.

The subject matter is well arranged; the discussions are informal. However, they present a vast amount of information in which the theoretic considerations are combined with the practical.

The pediatrician will be particularly interested in the chapter on normal personality development. It is well written and expresses a common sense point of view.

This textbook is recommended to every practicing physician who is and who should be interested in modern medical thinking.

Eleménts de puériculture à l'usage des étudiants et des infirmières des éducateurs et des parents: La, formation du corps et de l'esprit de l'enfant. By B. Weill-Hallé. Price, 450 francs. Pp. 260, with no illustrations. Paris: L'Expansion scientifique française, 1947.

The author brings to this study a warm understanding of the growing child and years of experience in the School of Puericulture of the Université de Paris Faculté de Médecine. Puericulture means for him the best efforts to provide background and stimuli which will help in developing a harmonious personality, physically fit, emotionally sound and intellectually alive. This embraces the assurance of healthy parentage and of optimum nutrition during the period of gestation, the avoidance of harmful incidents at birth, a favorable physical and emotional environment during childhood, with protection against disease and bad environmental influences, and, finally, participation in the child's orientation at the time of adolescence.

The first section of the book deals with growth, nutritional needs and immunization procedures; the second section with the awakening of the child's intel-

lect and the responsibilities of parents, teachers, nurses and physicians in the sphere of his development.

Throughout the book, one is aware of the generous personality of the author and his desire to share what he has learned in helping to bring about happier and more responsible coming generations. Although he is aware of the necessity for political and social changes and deprecates the inertia of governments in this field, his words are addressed particularly to persons who form the immediate environment of the child. They are words of detailed counsel, never arbitrary, but firm and definite, giving understanding and encouragement.

Twentieth Century Speech and Voice Correction. Edited by Emil Fröschels, M.D. Price, $6. Pp. 321, with 32 illustrations. New York: The Philosophical Library, Inc., 1948.

Nineteen authors contributed twenty-four essays on the anatomy, physiology and pathology of voice and speech. Among the speech disorders covered are aphasia, paragrammatism, infantile psychic deafness, acoustic disorders and treatment, rhinolalia, stuttering, cluttering and articulatory disorders resulting from gunshot injuries. Material on remedial reading and retraining of the speaking voice after laryngectomies is also included.

The editor states frankly that he made no attempt to correct inconsistencies among the various authors. Further, some of the essays are annotated and include bibliographies, and others lack these features. The result is a more or less uneven style.

Each essayist in turn is somewhat of a "special pleader," and the compilation might be quite confusing, as well as misleading, to a person not professionally trained in the field of voice and speech correction, since many of the authors were so limited in space that the didactic approach could not be used.

On the other hand, the material is stimulating and vigorous, and if the book is read with constant reference to broader texts, it may well prove useful. The pediatrician in general practice may find material in this collection to help him understand some of the problems of linguistic disorders in childhood; such a result alone would justify the publication of the book.

Current Trends in Clinical Psychology. By A. W. Combs, H. E. Durkin, M. L. Hutt, J. G. Miller, J. L. Moreno and F. C. Thorne. Annals of the New York Academy of Sciences, volume 49, article 6. Price, $1.50. Pp. 62, with no illustrations. New York: The New York Academy of Sciences, 1948.

This is a reprint of a series of papers presented at a conference on current trends in clinical psychology, held by the Section on Psychology of the New York Academy of Sciences.

The articles are principally devoted to a discussion of the differences between the so-called directive and nondirective technics in psychotherapy and the uses of group psychotherapy and psychodrama. The essayists are adherents of these respective technics and are prominent in the field of clinical psychology. The relation of clinical psychology to medical psychiatry is set forth in the final paper of this series.

This pamphlet has more historic than practical value for the physician. It may be of interest to those who have had training and experience in psychotherapy.

Hemorrhage. By Gregory Shwartzman, M.D., and others. Annals of the New York Academy of Sciences, volume 49, article 4. Price $3. Pp. 178, with 5 pages photomicrographs, 52 tables and 19 graphs. New York: New York Academy of Sciences, 1948.

This monograph contains fifteen articles on the control of hemorrhagic shock and is an endeavor to bring the newer knowledge in this field into correlated channels. These articles include reports on coagulation and blood clotting in general, both under normal conditions and under the influence of drugs, by means of surveys of the circulatory phenomena associated with hemorrhage. The subject matter is presented in a concise and readable manner. The articles are profusely illustrated with tables, graphs and photomicrographs. Both the clinician and the experimentalist present their observations, which are made more interesting by the inclusion of the discussion at the academy's conference on hemorrhage. This volume should be read with profit by all those interested in the subject of coagulation.

Diseases of the Ear, Nose and Throat. By William Wallace Morrison, M.D. Price, $8.50. Pp. 772, with 650 illustrations. New York: Appleton-Century-Crofts, Inc., 1948.

This volume fulfils well its purpose: to "inform the student and general practitioner of those things he should know to get the patient well." The book is practical and concise but does not omit essential details. It is unusually up to date. It is clear, easily readable and well organized; subheadings make finding desired information easy. For a book of this scope, especially good treatment has been given nasal allergy, headaches and neuralgias. Emphasis is on common conditions, but enough description of the rarer diseases is given to identify them.

There are many graphic illustrations, mostly drawings by the author. The volume should prove of great practical value to those for whom it was written.

Reflessi sociali della tonsillectomia; Osservazioni sulle persone senza tonsille. By Guido Calderoni, M.D. Price, 200 lire. Pp. 77. Bergamo, Italy: Tipografia F. LLI Carrara, 1947.

This is the fourth monograph by Calderoni on the tonsil problem. He recognizes a syndrome seen in a person whose tonsils have been removed which has certain similarities to the syndrome of agonadism. He cites cases to substantiate his theory that tonsillectomy will interfere with the normal interrelations of the endocrine glands, so as to result in a clinical syndrome characterized by a loss of energy and strength, an impairment of memory and changes in personality. He suggests that removal of part of the tonsils is much safer than complete tonsillectomy.

The reviewer believes the clinical data are too meager and sketchy to justify this philippic against tonsillectomy.

The 1948 Year Book of Pediatrics. Edited by Henry G. Poncher, M.D. Price, $4.50. Pp. 542, with 167 illustrations. Chicago: The Year Book Publishers, Inc., 1948.

This 1948 edition of "The Year Book of Pediatrics" is the first to appear under the editorship of Dr. Poncher. In content, format and arrangement it is unchanged, with the exception of somewhat more extensive editorial comment, which this reviewer considers an asset. Dr. Poncher has done an excellent job. He states

in his preface that he does not consider the form and content of the "Year Book" to be unchangeable, and it is to be expected that such changes as are made will be improvements.

As always, the "Year Book" is a valuable addition to the busy practitioner's library.

Acrodinia infantil. By Juan P. Garrahan and Rafael R. L. Sampayo. No price given. Pp. 94. Buenos Aires, Argentina: "El Ateneo," Liberia Cientifica y Literatia, 1947.

This monograph on the subject of infantile acrodynia at the outset gives the various names that have been applied to this condition in different countries. The authors use the term infantile to distinguish this type from that seen in an epidemic described by Chardon in Paris in 1827. The epidemic type affected adults and produced an erythema on the palms and the soles. Garrahan and Sampayo go back into the history of the disease, taking up the etiologic factors, the symptoms, the pathologic changes and the treatment. They cover every phase of treatment that has ever been recommended. Nothing new is offered but practically everything written on the disease since it was first described, down to the present, is reviewed, and a complete bibliography is given. Anyone interested in this subject, who can read Spanish, will find the subject well covered in this monograph.

The Problem of Cerebral Palsy Today. By M. A. Perlstein, M.D. Price, $0.25. Pp. 57. New York: Association for the Aid of Crippled Children, 1948.

A comprehensive survey of the problems of cerebral palsy is contained in this very readable monograph. The author gives an objective and broadminded appraisal of the existing methods used in diagnosis and treatment of persons with cerebral palsy and suggests desirable avenues of research.

The contents also include a well conceived state program, a section on professional training and a discussion of cerebral palsy as a socioeconomic problem.

This monograph will prove to be of value to members not only of the medical profession but also of other professions whose activities touch on this problem.

A Manual of Corrective Speech Exercises. By Nathanson and Nathanson. No price given. Pp. 36. Philadelphia: Jo Nathanson, 1947.

For the speech exercises given in this manual, 5,091 frequency words were selected, and an analysis was made of their basic sounds. These words were arranged to introduce apperceptively only one new sound at a time. The words are presented in 100 sections which fall into nine major groups, each section including illustrative sentences.

Essentials of Pathology. By Lawrence W. Smith, M.D., and Edwin S. Gault, M.D. Third edition. Price, $12. Pp. 764, with 740 illustrations. Philadelphia: The Blakiston Company, 1948.

This textbook offers a clear, concise presentation of the pathologic aspects of human diseases. It is most suitable for medical students who are being introduced to the subject. It is a better edition in many ways than the preceding one, for it is more comprehensive and more clearly written. Many illustrations are excellent.

Others need to be replaced, especially several in the sections dealing with systemic pathology. The format and systematic order of presentation of material should appeal strongly to the beginning student. Likewise, the series of well selected case histories, illustrating the relations between the clinical and pathologic aspects of many diseases should excite the student's interest. The bibliographic references are few in number but well chosen, representing in most instances authoritative references. There will never be a perfect textbook on pathology. Too much subject matter is involved. The correlation of practical clinical and adjunctive diagnostic or therapeutic knowledge with the more abstract knowledge and theory of the basic medical sciences is desirable. To accomplish this would seem an impossible task, but these authors, at least in some sections of their book, have made an effort. In this sense, they have come closer, at times, to writing a perfect textbook on pathology than anyone else.

Hospital Trends and Developments, 1940-1946. Edited by A. C. Bachmeyer and G. G. F. Hartman. Price, $5.50. Pp. 819, with no illustrations. New York: The Commonwealth Fund, 1948.

This is a reference book of particular value to persons in hospital administration. It is edited in the year book form without an attempt at extensive correlation of the articles therein. Only selective articles are presented. However, at the end of each chapter is an extensive reference bibliography. The various phases of hospital development are touched on throughout widely different fields. The following points are the more worth while in the reviewer's opinion: an excellent discussion on the subject of a voluntary compulsory health program; a discussion of the development and management of postwar medical problems in public health measures; a chapter on activities in relationship to rural hospital needs, and chapters on medical social workers and aspects of finance and legal control which give persons related to the hospital a much fairer concept of these subjects. The book is an excellent reference work for someone making a study of the problems of hospitals.

Directory of Pediatric Societies *

INTERNATIONAL

Sixth International Congress of Pediatrics

President: Prof. Guido Fanconi.
Secretary: Dr. H. Zellweger, Kinderklinik, Zurich.
American Committee:
President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave., New York 16.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. S. G. Ross, 1390 Sherbrooke St. W., Montreal.
Place: Zurich, Switzerland. Time: July 24-28, 1950.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

Pan American Congress of Pediatrics

President: Dr. Felix Hurtado, Habana, Cuba.

International Union for Child Welfare

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 43 Quay Wilson, Geneva, Switzerland.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Associação Paulista de Medicina, Secçaõ de Pediatrias

President: Dr. Armando de Arruda Sampaio.
First Secretary: Dr. Luis Fontoura y Lauro Machado Oliveira, Caixa Postal 2103, São Paulo, Brazil.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

Asociación Pediatrica de Guatemala

President: Dr. Carlos Manuel Monzon, Plazuela Santuario de Guadalupe, Guadalupe.
Secretary: Dr. Maria Isabel Escobar, Casa del Niño no. 1, Guadalupe.

British Paediatric Society

President: Dr. H. T. Ashby, 13 St. John St., Manchester, England.
Joint Secretary: Prof. Alan Moncrieff, Hospital for Sick Children, Great Ormond St., London W. C. 1.
Place: Windermere.

Bulgarian Pediatric Society

President: Dr. L. Ratchew, University Children's Hospital, Wassil Kolarow 46, Sofia.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Chinese Pediatric Society

President: Dr. W. S. Fu, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Secretary: Dr. T. F. Su, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Time: Concurrent with the annual conference of the Chinese Medical Association.

Czechoslovak Pediatric Society

Chairman: Prof. Dr. Jiri Brdlík, 2 Sokolská, Prague II.

Danish Pediatric Society

President: Prof. E. Lenstrup, Copenhagen.
Secretary: Dr. Gjørup, Dronning Louises Børnehospital, Copenhagen.

German Pediatric Society

President: Dr. H. Kleinschmidt.
Secretary: Dr. F. Goebel, 5 Moorenstrasse, Düsseldorf, Germany (British Zone).
Place: Düsseldorf. Time: September 1949.

Indian Pediatric Society

President: Dr. K. C. Chaudhuri, 56/2 Creek Row, Calcutta.
Secretary: Dr. N. G. Mojumdar, 29 Chakraberia Lane, Calcutta.

Nederlandsche Vereeninging voor Kindergeneeskunde

President: Dr. J. L. Keyzer, 114 St. Josephstr., Tilburg.
Secretary: Dr. H. Reerkink, % Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

Palestine Jewish Medical Association, Section of Physicans of Children's Diseases

President: Prof. L. F. Meyer, 29 Toelsohn St., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

Pediatric Society of New Zealand

President: Dr. Lawrence Ludbrook, The Lister Building, Victoria Street East, Auckland.

Royal Society of Medicine, Section for the Study of Diseases in Children

President: Prof. J. M. Smellie, 5 Flat, 8 Bolingbroke Grove, London S. W. 11.
Secretary: Dr. Mary Wilmers; Dr. R. Bonham Carter.
Place: 1 Wimpole St., London W. 1. Time: Fourth Friday of each month, 4:15 p. m.

Schweizerische Gesellschaft für Pädiatrie

President: Prof. Dr. A. Hottinger, Petersplatz 12, Basel.
Secretary: Dr. F. Hauser, Kinderspital, Basel.

Sociedad Boliviana de Pediatria

President: Dr. Carlos Ferrufino, Casilla 272, La Paz, Bolivia.
Secretary: Dr. Cecilio Abela D., Casilla 272, La Paz, Bolivia.
Place: S. C. I. S. P. Bldg. Time: Every Thursday.

Sociedad Chilena de Pediatria

President: Mr. Raúl Matte, Santiago, Chile.
General Secretary: Dr. Mariano Latorre, Santiago, Chile.
Place: Medical Society, Santiago, Chile. Time: 7:30 p. m., weekly.

Sociedad Cubana de Pediatria

President: Prof. Agustin Castellanos.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: 9 p. m., last Wednesday of every month.

SOCIEDAD DOMINICANA DE PEDIATRIA

President: Dr. Alberto Peguero, Avenida Bolivar 117, Ciudad Trujillo, R.D.
Secretary-Treasurer: Dr. Jaime Jorge, Lea de Castro 19, Ciudad Trujillo, R.D.
Place: Children's Ramfis Hospital. Time: 8 p. m., last Friday of every month.

SOCIEDAD ECUATORIANA DE PEDIATRIA

President: Dr. Alfredo Ceballos Carrión.
Secretary: Dr. Rafael Compte Andrade, P. O. Box 3480, Guayaquil.
Place: Hospital Central. Time: 11:30 a. m., every Friday.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Jesus Avarez de los Cobos.
Secretary: Dr. Luis Torregrosa F.
Place: Hospital Infantil. Time: Last Thursday of every month.

SOCIEDAD DE PEDIATRÍA DE CONCEPCIÓN (CHILE)

President: Dr. Raúl Ortega A., Hospital Clínico Regional, Concepción.
Secretary: Dr. Fidel Urrutia, Hospital Clínico Regional, Concepción.
Place: Hospital Clínico Regional, Concepción. Time: 7:30 p. m., second Tuesday of every month from April to December, inclusive.

SOCIEDAD DE PEDIATRÍA DE CÓRDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Albino F. Dottori, Dean Fumes 2000, Esq. Ocaña (N.), Córdoba, Argentina.
Place: Comite pro Defenso del Niño, Dean Fumes 2000, Córdoba, Argentina.
Time: Once a month.

SOCIEDAD DE PEDIATRIA DEL LITORAL

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

SOCIEDAD DE PEDIATRÍA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

SOCIEDADE PORTUGUÊSA DE PEDIATRIA

President: Prof. Almeida Garret.
Secretary: Dr. Cordeiro Ferreira, Hospital de D. Estefania, Lisbon.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Pastor Oropeza, Caracas.
Secretary: Dr. Guillermo Flores, Chacin, Sur 17, no. 26-2, Caracas.
Place: Hospital Municipal de Niños, Caracas. Time: Once a month.

SOCIEDAD YUCATECA DE PEDIATRIA

President: Dr. José Lavalle, Yucatan, Mexico.
Secretary: Dr. Francisco Solís, Yucatan, Mexico.
Place: Hospital del Niño, Yucatan, Mexico.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. G. Heuyer, 1 Ave. Emile Deschanel, Paris 7e, France.
Secretary: Dr. Maurice Lamy, 94 rue de Varenne, Paris 7e, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

SOCIETÉ POLONAISE DE PÉDIATRIE

President: Dr. Jan Bogdanowicz, Dzialdowska 1, Warsaw.
Secretary: Dr. Zofia Leimbach, Mieroslawskiego 9 m.6, Warsaw.

SOUTH AFRICAN PAEDIATRIC ASSOCIATION

Chairman: Dr. Basil Melle, 89 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.

Secretary-Treasurer: Dr. Seymour Heymann, 17 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.

SWEDISH ASSOCIATION OF PEDIATRICS

President: Prof. A. Lichtenstein, Crown Princess Louise's Children's Hospital, 30 Polhemsgata, Stockholm.

Secretary: Dr. K. A. Melin, Farjestadsvägen 16, Ängby.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Dr. R. Hybbinette, Kommendorsgatan 3, Stockholm.

Secretary: Dr. B. Broman, Eriksbergsgatan 1A, Stockholm.

Place: Various clinics and hospitals in Stockholm and Uppsala. Time: Second Friday of each month (except summer).

URUGUAYAN SOCETY OF PEDIATRICS

President: Dr. Héctor C. Bazzano.

Secretary: Dr. José M. Portillo.

Place: Club Medico del Uruguay, Avenida Agraciada 1464 (Piso 13), Montevideo.

VIENNA PEDIATRIC SOCIETY

President: Prof. Dr. A. Solé, Karolinen-Kinderspital, Sobieskigasse 31, Vienna 9.

Secretary: Doz. Dr. Asperger, Universitäts-Kinderklinik, Lazarettgasse 14, Vienna 9.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY. SECTION ON PEDIATRICS

Chairman: Dr. Woodruff L. Crawford, 321 W. State St., Rockford, Ill.

Secretary: Dr. Margaret Mary Nicholson, 1801 Eye St. N. W., Washington, D. C.

Place: Atlantic City, N. J. Time: June 6-10, 1949.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Warren R. Sisson, 319 Longwood Ave., Boston 15.

Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.

Place: Atlanta, Ga. Time: April 13-15, 1949.

Annual Meeting: Place: San Francisco. Time: Nov. 14-17, 1949.

AMERICAN HOSPITAL ASSOCIATION, MASSACHUSETTS HOSPITAL ASSOCIATION

Chairman: Dr. Frank Wing, Boston.

Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Valjean Cooke, 8700 Argyle Ave., St. Louis.

Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.

Place: Atlantic City. Time: May 3-5 (?), 1949.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. P. E. Williams, 193 James St. S., Hamilton, Ontario.

Secretary-Treasurer: Dr. R. L. Denton, 1615 Cedar Ave., Montreal.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. Sidney Farber, 300 Longwood Ave., Boston.

Secretary: Dr. Robert Ward, Bellevue Hospital, New York 16.

SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Spencer Snow, 75 S. Main St., Salt Lake City.

Secretary-Treasurer: Dr. Esther Gross, 202 E. South Temple St., Salt Lake City.

Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. Howard W. Brayton, 179 Allyn Street, Hartford 3, Conn.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. Clarence L. Lyon, 407 Riverside Ave., Spokane 8, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. Paul Bancroft, 909 Sharp Bldg., Lincoln, Neb.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. William D. Rothwell Jr., Republic Bldg., Denver.
Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.
Place: Children's Hospital of the Colorado General Hospital. Time: Monthly from October to June.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. Carroll M. Pounders, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. W. A. Daniel Jr., 115 S. Union St., Montgomery 5, Ala.
Secretary-Treasurer: Dr. D. B. Monsky, 905 Norman Bridge Rd., Montgomery 6, Ala.
Place: Montgomery, Ala. Time: September 1949.

ARIZONA PEDIATRIC SOCIETY

President: Dr. Hugh Thompson Jr., 110 S. Scott St., Tucson, Ariz.
Secretary: Dr. James R. Sickler, Physicians Bldg., Tucson, Ariz.
Place: Phoenix or Tucson. Time: On call.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Alice Potter, 1418 Ninth Ave., San Francisco 22.
Secretary: Dr. Carl Erickson, 595 E. Colorado, Pasadena.
Place: Los Angeles. Time: April 1949.

FLORIDA STATE PEDIATRIC SOCIETY

President: Dr. Edgar W. Stephens, 910 Harvey Bldg., West Palm Beach.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

GEORGIA PEDIATRIC SOCIETY

President: Dr. Lee Bivings, 20 Fourth St. N. W., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. H. L. F. Locke, 179 Allyn St., Hartford, Conn.
Secretary: Dr. L. W. Minor, 119 Main St., Middletown, Conn.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago 24.
Secretary: Dr. George L. Drennen, Jacksonville, Ill.
Place: Palmer House, Chicago. Time: May 10-12, 1949.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Charlotte Fisk, 1201 Equitable Bldg., Des Moines 9.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.
Place: Des Moines. Time: April 1949.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. William C. Rivenbank, 1448 Louisiana Ave., New Orleans 15.
Secretary-Treasurer: Dr. Bertha Wexler, 3439 Prytania St., New Orleans 15.
Place: New Orleans. Time: May 7, 1949.

MEDICAL SOCIETY OF THE STATE OF NEW YORK, PEDIATRIC SOCIETY

Chairman: Dr. Thurman B. Givan, 115 Remsen St., Brooklyn 2.
Secretary: Dr. Reginald A. Higgons, Port Chester.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. Waldo E. Nelson, Temple University, Philadelphia 40.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. H. J. Lewis, 2956 Biddle Ave., Wyandotte.
Secretary: Dr. Robert H. Trimby, 122 W. Hillsdale, Lansing.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Place, Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. George Clark, 1817 Vinton St., Omaha.
Secretary-Treasurer: Dr. Michael Crofoot, 1407 Medical Arts Bldg., Omaha 2.
Place: Children's Memorial Hospital. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW JERSEY MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Israel J. Wolf, 231 E. 31st St., Paterson.
Secretary: Dr. N. T. Crane, 147 E. 7th St., Plainfield, N. J.

NEW MEXICO STATE PEDIATRIC SOCIETY

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.
Secretary: Dr. Charles H. Gay, 1523 Elizabeth Ave., Charlotte, N. C.

NORTHERN CALIFORNIA PEDIATRIC SOCIETY

President: Dr. William C. Deamer, 3 Fifth Ave., San Francisco 18.
Secretary: Dr. A. L. Gleason, 1066 Longridge Rd., Oakland 10.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

PHILIPPINE PEDIATRIC SOCIETY

President: Dr. Alberto V. Tupas, Philippine General Hospital, Manila, Philippines.
Secretary: Dr. Artemio P. Jongco, Philippine General Hospital, Manila, Philippines.
Place: Philippine General Hospital. Time: Every two months.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. B. Owen Ravenel, 95 Rutledge Ave., Charleston 16.
Secretary-Treasurer: Dr. John R. Harvin, 206 N. Sumter St., Sumter.

TENNESSEE PEDIATRIC SOCIETY

President: Dr. W. O. Vaughan, 2103 Hayes St., Nashville 5.
Secretary-Treasurer: Dr. C. Barton Etter, 1678 Peach, Memphis 12.
Place: Chattanooga. Time: Second Monday in April.

TEXAS PEDIATRIC SOCIETY

President: Dr. John K. Glen, 4412 Montrose St., Houston.
Secretary-Treasurer: Dr. James N. Walker, 3616 Tulsa Way, Fort Worth 7.
Place: San Antonio. Time: Oct. 7-8, 1949.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. C. P. Brown, 142 W. York St.. Norfolk.
Secretary: Dr. E. Berkeley Neal, 303 Washington Ave. S. W., Roanoke.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. Thomas G. Folsom, 1139 Fourth Ave., Huntington.
Secretary: Dr. Warren J. Parsons, 425 Eleventh St., Huntington.

WISCONSIN STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2.
Secretary: Dr. L. M. Simonson, 1001 N. 8th St., Sheboygan.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. John Hart Davis, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Francis F. Silver, 9400 Euclid Ave., Cleveland.
Place: Allen Memorial Medical Library. Time: 8:15 p. m., October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. A. L. Chute, 170 St. George St., Toronto, Canada.
Secretary: Dr. John Fletcher, 262 St. Clair St. W., Toronto, Canada.
Place: Academy of Medicine. Time: 8:30 p. m., third Thursday of each month.

BALTIMORE CITY MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Charles O'Donovan Jr., 5 E. Read St., Baltimore.
Secretary: Dr. T. Campbell Goodwin, 16 E. Biddle St., Baltimore.

BRONX PEDIATRIC SOCIETY

President: Dr. Harry S. Pizer, 1726 Davidson Ave., New York.
Secretary: Dr. William A. Schonfeld, 211 W. 106th St., New York 25.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Walter R. Coles, 604–2d St., Brooklyn.
Secretary: Dr. Bernard Benjamin, 845 Park Pl., Brooklyn 16.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April, October and November.

BUFFALO PEDIATRIC SOCIETY

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. T. Wood Clarke, 7 Cottage Place, Utica.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Tuesday of April and October.

Chicago Pediatric Society

President: Dr. John L. Reichert, 1791 Howard St., Chicago 26.
Secretary: Dr. Alvah L. Newcomb, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

Cincinnati Pediatric Society

President: Dr. John H. Hunt, Kemper Lane Bldg., Cincinnati.
Secretary: Dr. William F. Hunting, 6048 Montgomery, Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. Guy Hacker, 5711 Goliad St., Dallas.
Secretary-Treasurer: Dr. George R. Branch, 4325 Cole Ave., Dallas.
Place: Children's Hospital of Texas and Bradford Memorial Hospital. Time: 1 p. m., third Saturday and 8:30 p. m., the first Tuesday of each month.

Detroit Pediatric Society

President: Dr. Harold B. Rothbart, 773 Fisher Bldg., Detroit 2.
Secretary: Dr. S. S. Bernstein, 650 Maccabees Bldg., Detroit.
Place: Variable. Time: Five times annually.

Fort Worth Pediatric Society

President: Dr. Frank Cohen, 712 S. Henderson, Fort Worth, Texas.
Secretary: Dr. H. H. Womack, 1422 Pennsylvania, Fort Worth, Texas.
Place: Welch and West Restaurant. Time: Third Friday of each month.

Honolulu Pediatric Society

President: Dr. Donald Marshall, Medical Group, Honolulu.
Secretary-Treasurer: Dr. Teruo Yoshina, 1221 Victoria St., Honolulu

Houston Pediatric Society

President: Dr. Edward O. Fitch, 3720 Fannin St., Houston, Texas.
Secretary: Dr. Thomas J. Donovan, 3506 Sunset Blvd., Houston 5, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., last Tuesday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Hoel Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

Knoxville-Oak Ridge Pediatric Society

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Secretary-Treasurer: Dr. Robert Simonds, 267 S. Beverly Dr., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Harold Levy, 750 St. Marks Ave., Brooklyn 16.
Secretary: Dr. Jacob J. Lichterman, 1433 Union St., Brooklyn 13.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. John Washington, 2032 Belmont Rd. N.W., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N.W. Time: Spring and fall.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. C. Barton Etter, 1678 Peach, Memphis 12, Tenn.
Secretary-Treasurer: Dr. Jacob Danciger, 188 S. Bellevue Blvd., Memphis 4, Tenn.
Place: University Center, 4 S. Dunlap. Time: 7 p. m., second Tuesday of every month.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. James Conway, 1721 E. Lake Bluff Blvd., Milwaukee 11, Wis.
Secretary-Treasurer: Dr. Walter Polacheck, 425 E. Wisconsin Ave., Milwaukee 2, Wis.
Place: City Club of Milwaukee. Time: Second Wednesday in February, April, June, October and December.

NASHVILLE PEDIATRIC SOCIETY

President: Dr. John M. Lee, Doctors Bldg., Nashville, Tenn.
Secretary: Dr. Dan S. Sanders Jr., 2103 Hayes St., Nashville, Tenn.
Time: Third Thursday of every month.

NEW YORK ACADEMY OF MEDICINE, SECTION ON PEDIATRICS

Chairman: Dr. John Dorsey Craig, 120 E. 75th St., New York 21.
Secretary: Dr. Morris Greenberg, 143 W. 87th St., New York.
Place: New York Academy of Medicine, 2 E. 103rd St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. Bertha M. Levy, 717 N. W. 22d St., Oklahoma City 3.
Secretary: Dr. C. M. Bielstein, 301 N. W. 12th St., Oklahoma City 3.
Place: Oklahoma Club. Time: On call.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. Milton Rapoport, 741 S. 3d St., Philadelphia.
Secretary: Dr. D. Stewart Polk, W. Montgomery Ave., Rosemont, Pa.
Place: College of Physicians, 19 S. 22nd St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. J. A. Gilmartin, 3708–15th Ave., Pittsburgh.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Municipal Hospital, Pittsburgh. Time: Second Friday in October, December, February and April.

QUEENS PEDIATRIC SOCIETY

Chairman: Dr. Walter C. A. Steffen, 42-28 Union St., Flushing, N. Y.
Secretary-Treasurer: Dr. Louis Appel, 33-03 Parsons Blvd., Flushing, N. Y.
Place: Forest Hills, N. Y. Time: Third Monday of October, February, April; first Monday of December.

RICHMOND PEDIATRIC SOCIETY

President: Dr. Thomas S. Chalkley, 421 W. Grace St., Richmond 20, Va.
Secretary-Treasurer: Dr. John Paul Jones, 810 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

ROCHESTER PEDIATRIC SOCIETY

President: Dr. Jerome Glaser, 85 San Gabriel Dr., Rochester 10, N. Y.
Secretary-Treasurer: Dr. Daniel B. Peeler, 1162 Lake Ave., Rochester 13, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee.
Time: Third Friday of each month from October to May.

ST. LOUIS PEDIATRIC SOCIETY

President: Dr. Merl J. Carson, 500 S. Kingshighway, St. Louis.
Secretary-Treasurer: Dr. Jackson K. Eto, 734 Missouri Theatre Bldg., St. Louis 3.
Place: Hotel Branscome. Time: Second Thursday of each month from October to May, inclusive, 6:30 p. m.

San Antonio Pediatric Society

President: Dr. Lucius Hill, 328 Medical Arts Bldg., San Antonio 5.
Secretary-Treasurer: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Place: Bexar County Medical Library. Time: 7:30 p. m., first Tuesday of every month.

Seattle Pediatric Society

President: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle 1.
Secretary: Dr. Jack M. Doctor, 738 Broadway, Seattle 22.
Place: College Club. Time: Fourth Friday of each month from September to June at 6:30 p m.

Southwestern Pediatric Society

President: Dr. Harry F. Dietrich, 416 N. Bedford Dr., Beverly Hills, Calif.
Secretary: Dr. Clement H. Maloney, Beverly Hills, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., second Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Ernest H. Watson, University Hospital, Ann Arbor.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor.

Waco Pediatric Society

President: Dr. M. C. Carlisle, 1410 Austin Ave., Waco, Texas.
Secretary: Dr. F. W. Hoehn, 1422 Austin Ave., Waco, Texas.
Place: Provident Hospital, 1725 Colcord, Waco, Texas. Time: Third Thursday of each month.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. Harry W. Kaessler, 147 Prospect Ave., Mount Vernon, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Fourth Thursday of every other month from September to June (dinner meetings).